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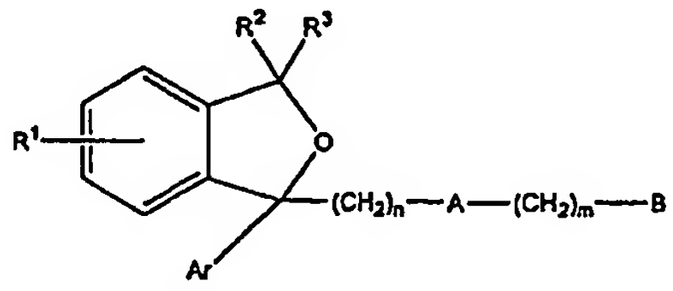


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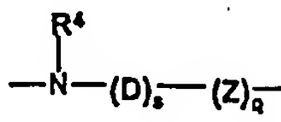


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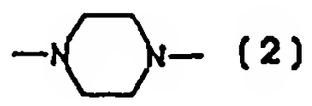

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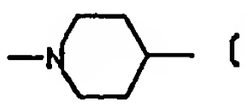

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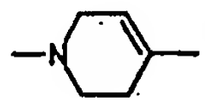

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(57) Abstract

The present invention relates to benzofuran derivatives having general Formula (I). A is selected from (1), (2), (3), (4) wherein: Z is O or S; s is 0 or 1; q is 0 or 1; $R^4$ is hydrogen, $C_{1-6}$–alkyl, $C_{2-6}$–alkenyl, $C_{2-6}$–alkynyl, $C_{1-6}$–alkyl–Aryl, or $C_{1-6}$–alkyl–O–Aryl; D is a spacer group selected from branched or straight chain $C_{1-6}$–alkylene, $C_{2-6}$–alkenylene and $C_{2-6}$–alkynylene; its enantiomers, and pharmaceutically acceptable acid addition salt thereof. The compounds are potently binding to the 5–$HT_{1A}$ receptor.

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# Benzofuran derivatives, their preparation and use

The present invention relates to novel benzofuran derivatives potently binding to the 5-$HT_{1A}$ receptor, pharmaceutical compositions containing these compounds and the use thereof for the treatment of certain psychiatric and neurological disorders. Many of the compounds of the invention are also potent serotonin reuptake inhibitors and are considered to be particularly useful for the treatment of depression.

## Background Art

Clinical studies of known 5-$HT_{1A}$ partial agonists such as e.g. buspirone, ipsapirone and gepirone have shown that 5-$HT_{1A}$ partial agonists are useful in the treatment of anxiety disorders such as generalised anxiety disorder, panic disorder, and obsessive compulsive disorder (Glitz, D. A., Pohl, R., *Drugs* 1991, *41*, 11). Preclinical studies indicate that full agonists also are useful in the treatment of the above mentioned anxiety related disorders (Schipper, *Human Psychopharm.*, 1991, *6*, S53).

There is also evidence, both clinical and preclinical, in support of a beneficial effect of 5-$HT_{1A}$ partial agonists in the treatment of depression as well as impulse control disorders and alcohol abuse (van Hest, *Psychopharm.*, 1992, *107*, 474; Schipper et al, *Human Psychopharm.*, 1991, *6*, S53; Cervo et al, *Eur. J. Pharm.*, 1988, *158*, 53; Glitz, D. A., Pohl, R., *Drugs* 1991, *41*, 11; Grof et al., *Int. Clin. Psychopharmacol.* 1993, *8*, 167-172; Ansseau et al., *Human Psychopharmacol.* 1993, *8*, 279-283).

5-$HT_{1A}$ agonists and partial agonists inhibit isolation-induced aggression in male mice indicating that these compounds are useful in the treatment of aggression (Sanchéz et al, *Psychopharmacology*, 1993, *110*, 53-59).

Furthermore, 5-$HT_{1A}$ agonists have been reported to show activity in animal models predictive for antipsychotic effects (Wadenberg and Ahlenius, *J. Neural. Transm.*, 1991, *83*, 43; Ahlenius, *Pharmacol. & Toxicol.*, 1989, *64*, 3; Lowe et al., *J. Med. Chem.*, 1991, *34*, 1860; New et al., *J. Med. Chem.*, 1989, *32*, 1147; and Martin et al., *J. Med. Chem.*,

1989, *32*, 1052) and may therefore be useful in the treatment of psychotic disorders such as schizophrenia. Recent studies also indicate that 5-$HT_{1A}$ receptors are important in the serotonergic modulation of haloperidol-induced catalepsy (Hicks, *Life Science* 1990, *47*, 1609) suggesting that 5-$HT_{1A}$ agonists are useful in the treatment of the side effects induced by conventional antipsychotic agents such as e.g. haloperidol.

5-$HT_{1A}$ agonists have shown neuroprotective properties in rodent models of focal and global cerebral ischaemia and may, therefore, be useful in the treatment of ischaemic disease states (Prehn , *Eur. J. Pharm.* 1991, *203*, 213).

Pharmacological studies have been presented which indicate that 5-$HT_{1A}$ antagonists are useful in the treatment of senile dementia (Bowen et al., Trends Neur. Sci. 1992, *15*, 84).

An overview of 5-$HT_{1A}$ antagonists and proposed potential therapeutic targets for these antagonists based upon preclinical and clinical data are presented by Schechter et al., *Serotonin*, 1997, Vol.2, Issue 7. It is stated that 5-$HT_{1A}$ antagonists may be useful in the treatment of schizophrenia, dementia associated with Alzheimer's disease, and in combination with SSRI antidepressants also to be useful in the treatment of depression.

Both in animal models and in clinical trials it has been shown that 5-$HT_{1A}$ agonists exert antihypertensive effects *via* a central mechanism (Saxena and Villalón, *Trends Pharm. Sci.* 1990, *11*, 95; Gillis *et al, J. Pharm. Exp. Ther.* 1989, *248*, 851). 5-$HT_{1A}$ ligands may, therefore, be beneficial in the treatment of cardiovascular disorders.

5-HT reuptake inhibitors are well known antidepressant drugs and useful for the treatment of panic disorders and social phobia.

The effect of combined administration of a compound that inhibits serotonin reuptake and a 5-$HT_{1A}$ receptor antagonist has been evaluated in several studies (Innis, R.B. et al., *Eur. J. Pharmacol.*, **1987**, *143, p 195-204* and Gartside, S.E., *Br. J. Pharmacol.* **1995**, *115, p 1064-1070,* Blier, P. *et al, Trends Pharmacol. Sci.* **1994**, *15*, 220). In these studies it was found that 5-$HT_{1A}$ receptor antagonists would abolish the initial brake on 5-HT

neurotransmission induced by the serotonin reuptake inhibitors and thus produce an immediate boost of 5-HT transmission and a more rapid onset of therapeutic action.

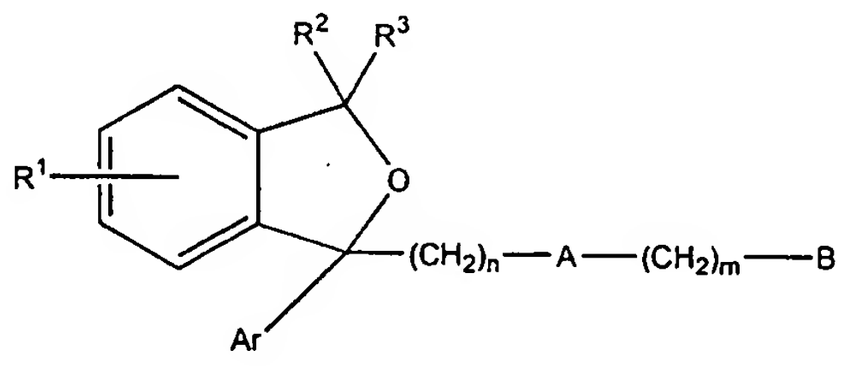
Several patent applications have been filed which cover the use of a combination of a 5-$HT_{1A}$ antagonist and a serotonin reuptake inhibitor for the treatment of depression (see EP-A2-687 472 and EP-A2-714 663).

Accordingly, agents acting on the 5-$HT_{1A}$ receptor, both agonists and antagonists, are believed to be of potential use in the therapy of psychiatric and neurological disorders and thus being highly desired. Furthermore, antagonists at the same time having potent serotonin reuptake inhibition activity may be useful for the treatment of depression.

**Summary of the Invention**

It has now been found that compounds of a certain class of benzofuran derivatives bind to the 5-$HT_{1A}$ receptor with high affinities. Furthermore, it has been found that many of these compounds have potent serotonin reuptake inhibition activity.

Accordingly, the present invention relates to novel compounds of the general Formula I:




(I)

wherein

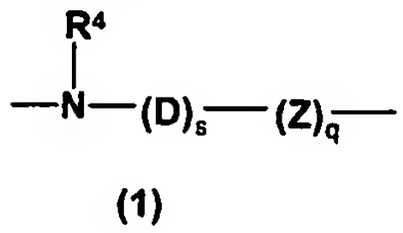
$R^1$ is hydrogen, halogen, trifluoromethyl, trifluoromethylsulfonyloxy, $C_{1-6}$ alkyl, $C_{2-6}$ alkenyl, $C_{2-6}$ alkynyl, $C_{3-8}$ cycloalkyl, $C_{1-6}$ alkoxy, hydroxy, formyl, acyl, amino, $C_{1-6}$ alkylamino, $C_{2-12}$ dialkylamino, acylamino, $C_{1-6}$ alkoxycarbonylamino, aminocarbonylamino, $C_{1-6}$ alkylaminocarbonylamino, $C_{2-12}$ dialkylaminocarbonylamino, nitro, cyano, COOH, or COO-$C_{1-6}$ alkyl;

$R^2$ and $R^3$ are each independently selected from hydrogen, trifluoromethyl, $C_{1-6}$ alkyl, $C_{2-6}$ alkenyl, $C_{2-6}$ alkynyl, $C_{3-8}$ cycloalkyl and $C_{1-6}$ alkoxy;

n is 1, 2, 3, 4 or 5;

m is 0 or 1;

A is selected from the following groups:



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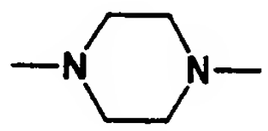

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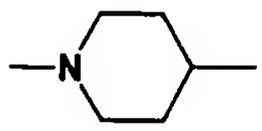

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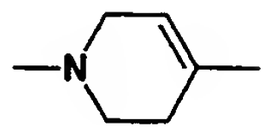


(4)

wherein

Z is O or S;

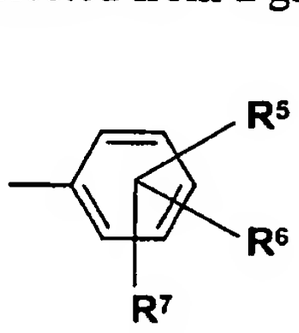
s is 0 or 1;

q is 0 or 1;

$R^4$ is hydrogen, $C_{1-6}$-alkyl, $C_{2-6}$-alkenyl, $C_{2-6}$-alkynyl, $C_{1-6}$-alkyl-Aryl, or $C_{1-6}$-alkyl-O-Aryl,

D is a spacer group selected from branched or straight chain $C_{1-6}$-alkylene, $C_{2-6}$-alkenylene and $C_{2-6}$-alkynylene;

B is a group selected from a group of formula (II), (III), and (IV)



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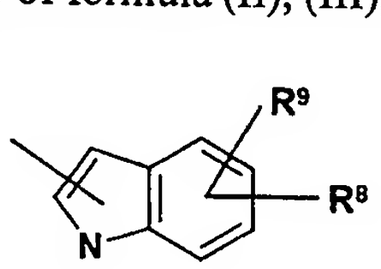

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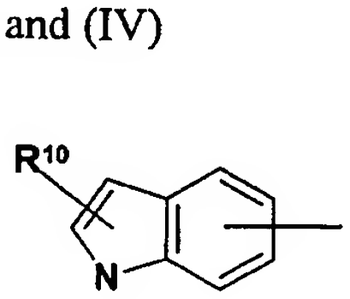


(IV)

wherein $R^5$, $R^6$, $R^7$, $R^8$, $R^9$ and $R^{10}$ are each independently selected among the $R^1$ substituents;

or $R^8$ and $R^9$ together form a fused 5- or 6-membered ring optionally containing further heteroatoms;

or two of the groups of $R^5$, $R^6$ and $R^7$ are linked together thereby forming a $—O—(CH_2)_p—O—$ -bridge wherein p is 1 or 2;

Ar and Aryl are independently selected from the group consisting of phenyl, 2–thienyl, 3–thienyl, 2–furanyl, 3–furanyl, 2–pyrimidyl, 1–indolyl, 2–indolyl, 3–indolyl, indol-2-on-1-yl, indol-2-on-3-yl, 2- or 3–benzofuranyl, 2- or 3–benzothiophenyl, 1–naphthyl or 2–naphthyl, each optionally substituted with halogen, $C_{1-6}$ alkyl, $C_{1-6}$ alkoxy, $C_{1-6}$ alkylthio, hydroxy, $C_{1-6}$ alkylsulfonyl, cyano, trifluoromethyl, trifluoromethylsulfonyloxy, $C_{3-8}$ cycloalkyl, $C_{3-8}$ cycloalkyl–$C_{1-6}$ alkyl, nitro, amino, $C_{1-6}$ alkylamino, $C_{2-12}$ dialkylamino, acylamino or alkylenedioxy;

its enantiomers, and pharmaceutically acceptable acid addition salt thereof.

In one embodiment of the invention A is a group of formula (1) and the other substituents are as defined above.

In another embodiment of the invention A is a group of formula (2) and the other substituents are as defined above.

In a third embodiment of the invention A is a group of formula (3) and the other substituents are as defined above.

In a fourth embodiment of the invention A is a group of formula (4) and the other substituents are as defined above.

Thus in a preferred embodiment of the invention A is a group of formula (1) and $R^4$ is methyl, ethyl, propyl, prop-2-en-1-yl, 2-furylmethyl, or 2-phenoxyethyl; q = 0; or A is a group of formula (1) and Z is O and the other substituents are as defined above.

In a further embodiment of the invention, B is a group of formula (II), preferably a alkoxysubstituted phenyl, a benzodioxan group or a 1,2-methylenedioxybenzene group and the other substituents are as defined above.

In a further embodiment of the invention, B is a group of formula (III), preferably a 3-indolyl group and the other substituents are as defined above.

In a further embodiment of the invention, B is a group of formula (III), preferably a 3-indolyl group and the substituents $R^8$ and $R^9$ are preferably selected from hydrogen, methyl, fluoro, chloro, bromo, iodo, *t*-butyl or *i*-propyl in the 5-position; or fluoro, chloro or carboxy in the 7-position; or by 5,7-difluoro, 4-fluoro-7-methyl or 4-chloro-7-methyl; or the two substituents together form a pyridyl ring fused to the 3-indolyl.

In a further embodiment of the invention, B is a group of formula (IV) and the other substituents are as defined above.

Ar is preferably phenyl or phenyl substituted with halogen or $CF_3$, most preferably substituted with F or Cl in the 4-position or Cl or $CF_3$ in the 3-position.

$R^1$ is preferably H, CN or F in the 5-position of the isobenzofuran group.

$R^2$ and $R^3$ are preferably selected from hydrogen or methyl.

n is preferably 2, 3 or 4.

m is preferably 0.

In a preferred embodiment of the invention n = 2, 3 or 4; $R^2$ and $R^3$ are both hydrogen; $R^1$ is H, CN or F in the 5-position of the isobenzofuran group; and Ar is phenyl which may be substituted with F or Cl in the 4-position or with Cl or $CF_3$ in the 3-position and the other substituents are as defined above.

In another preferred embodiment of the invention, A is a group of formula (1); q = 0; $R^4$ is methyl; D is propylene; m = 0; and B is a 1,4-benzodioxan group of Formula (II) attached in the 5-position and the other substituents are as defined above.

In another preferred embodiment of the invention, A is a group of formula (1); $R^4$ is $CH_3$ or prop-2-en-1-yl; n = 3; D is ethylene or propylene; and B is a phenyl group wherein at least one substituent is OMe and the other substituents are as defined above.

In a further embodiment of the invention, A is a group of formula (1); q is 0; $R^4$ is methyl, ethyl, propyl, 2-propen-1-yl, 2-furylmethyl or 2-phenoxyethyl; D is ethylene, propylene or butylene; m = 0; and B is a 3-indolyl group of Formula (III) and the other substituents are as defined above.

In another preferred embodiment of the invention, A is a group of formula (2) or (3); n = 3; m = 0; and B is an 4- or 5-indolyl-group of Formula (IV) wherein $R^{10}$ is hydrogen; $R^1$ is CN in the 5-position of the isobenzofuran and Ar is 4-Fluorophenyl and the other substituents are as defined above.

The invention also relates to a pharmaceutical composition comprising a compound of formula (I) or a pharmaceutically acceptable salt thereof and at least one pharmaceutically acceptable carrier or diluent.

In a further embodiment, the invention relates to the use of a compound of formula (I) or a pharmaceutically acceptable acid addition salt thereof for the preparation of a medicament for the treatment of a disorder or disease responsive to the effect of 5-$HT_{1A}$ receptors.

In particular, the invention relates to the use of a compound according to the invention or a pharmaceutically acceptable acid addition salt thereof for the preparation of a medicament for the treatment of depression, psychosis, anxiety disorders, panic disorder, obsessive compulsive disorder, impulse control disorder, alcohol abuse, aggression, ischaemia, senile dementia, cardiovascular disorders or social phobia.

In still another embodiment, the present invention relates to a method for the treatment of a disorder or disease of living animal body, including a human, which is responsive to the effect of 5-$HT_{1A}$ receptors comprising administering to such a living animal body, including a human, a therapeutically effective amount of a compound of formula (I) or a pharmaceutically acceptable acid addition salt thereof.

The compounds of the invention have high affinity for the 5-$HT_{1A}$ receptor. Accordingly, the compounds of the invention are considered useful for the treatment of depression, psychosis, anxiety disorders, such as generalised anxiety disorder, panic disorder, and obsessive compulsive disorder, impulse control disorder, alcohol abuse, aggression, ischaemia, senile dementia, cardiovascular disorders and social phobia.

Due to their combined antagonism of 5-$HT_{1A}$ receptors and serotonin reuptake inhibiting effect, many of the compounds of the invention are considered particularly useful as fast onset of action medicaments for the treatment of depression. The compounds may also be useful for the treatment of depression in patients who are resistant to treatment with currently available antidepressants.

**Detailed Description of the Invention**

Some of the compounds of general Formula I may exist as optical isomers thereof and such optical isomers are also embraced by the invention.

The term $C_{1-6}$ alkyl refers to a branched or unbranched alkyl group having from one to six carbon atoms inclusive, such as methyl, ethyl, 1-propyl, 2-propyl, 1-butyl, 2-butyl, 2-methyl-2-propyl and 2-methyl-1-propyl.

Similarly, $C_{2-6}$ alkenyl and $C_{2-6}$ alkynyl, respectively, designate such groups having from two to six carbon atoms, inclusive.

Halogen means fluoro, chloro, bromo, or iodo.

The term $C_{3-8}$ cycloalkyl designates a monocyclic or bicyclic carbocycle having three to eight C-atoms, such as cyclopropyl, cyclopentyl, cyclohexyl, cycloheptyl, and cyclooctyl.

The terms $C_{1-6}$ alkoxy, $C_{1-6}$ alkylthio, $C_{1-6}$ alkylsulfonyl, designate such groups in which the alkyl group is $C_{1-6}$ alkyl as defined above.

Acyl means -CO-alkyl wherein the alkyl group is $C_{1-6}$ alkyl as defined above.

$C_{1-6}$ alkylamino means -NH-alkyl, and $C_{2-12}$ dialkylamino means -N-$(alkyl)_2$ where the alkyl group is $C_{1-6}$ alkyl as defined above.

Acylamino means -NH-acyl wherein acyl is as defined above.

$C_{1-6}$ alkoxycarbonylamino means alkyl-O-CO-NH- wherein the alkyl group is $C_{1-6}$ alkyl as defined above.

$C_{1-6}$ alkylaminocarbonylamino means alkyl-NH-CO-NH- wherein the alkyl group is $C_{1-6}$ alkyl as defined above.

$C_{2-12}$ dialkylaminocarbonylamino means $(alkyl)_2$-N-CO-NH- wherein the alkyl group is $C_{1-6}$ alkyl as defined above.

Exemplary of organic acid addition salts according to the invention are those with maleic, fumaric, benzoic, ascorbic, succinic, oxalic, bis-methylenesalicylic, methanesulfonic, ethanedisulfonic, acetic, propionic, tartaric, salicylic, citric, gluconic, lactic, malic, mandelic, cinnamic, citraconic, aspartic, stearic, palmitic, itaconic, glycolic, p-aminobenzoic, glutamic, benzenesulfonic, and theophylline acetic acids, as well as the 8-halotheophyllines, for example 8-bromotheophylline. Exemplary of inorganic acid addition salts according to the invention are those with hydrochloric, hydrobromic, sulfuric, sulfamic, phosphoric, and nitric acids. The acid addition salts of the invention are preferably pharmaceutically acceptable salts formed with non-toxic acids.

Furthermore, the compounds of this invention may exist in unsolvated as well as in solvated forms with pharmaceutically acceptable solvents such as water, ethanol and the like. In general, the solvated forms are considered equivalent to the unsolvated forms for the purposes of this invention.

Some of the compounds of the present invention contain chiral centres and such compounds exist in the form of isomers (e.g. enantiomers). The invention includes all such isomers and any mixtures thereof including racemic mixtures.

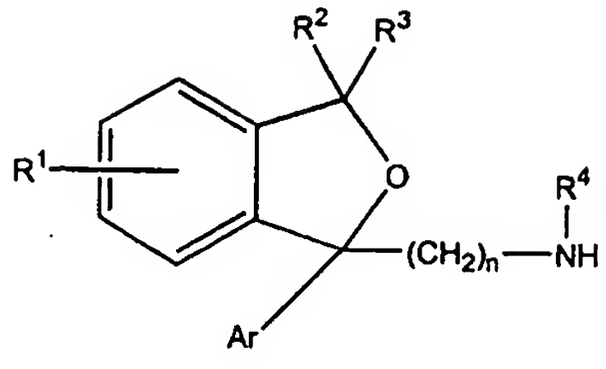
Racemic forms can be resolved into the optical antipodes by known methods, for example, by separation of diastereomeric salts thereof with an optically active acid, and liberating the optically active amine compound by treatment with a base. Another method for resolving racemates into the optical antipodes is based upon chromatography on an optically active matrix. Racemic compounds of the present invention can thus be resolved into their optical antipodes, e.g., by fractional crystallisation of d- or l- (tartrates, mandelates, or camphorsulphonate) salts for example. The compounds of the present invention may also be resolved by the formation of diastereomeric derivatives.

Additional methods for the resolution of optical isomers, known to those skilled in the art, may be used. Such methods include those discussed by J. Jaques, A. Collet, and S. Wilen in "Enantiomers, Racemates, and Resolutions", John Wiley and Sons, New York (1981).

Optically active compounds can also be prepared from optically active starting materials.

The compounds of the invention can be prepared by one of the following methods comprising:

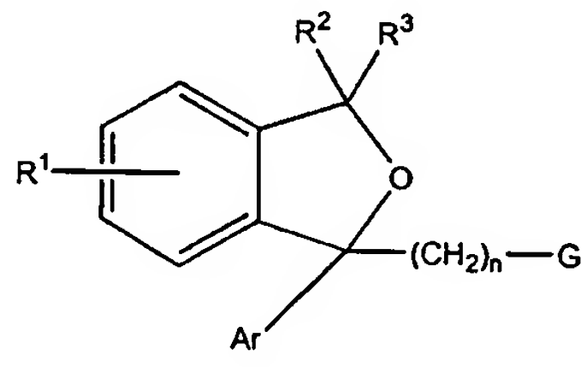
a) alkylating an amine of formula



(V)

wherein $R^1$, $R^2$, $R^3$, $R^4$, n and Ar are as defined above with an alkylating agent of formula $G-(D)_s-(Z)_q-(CH_2)_m-B$ wherein D, Z, m, s, q and B are as defined above and G is a suitable leaving group such as halogen, mesylate, or tosylate;

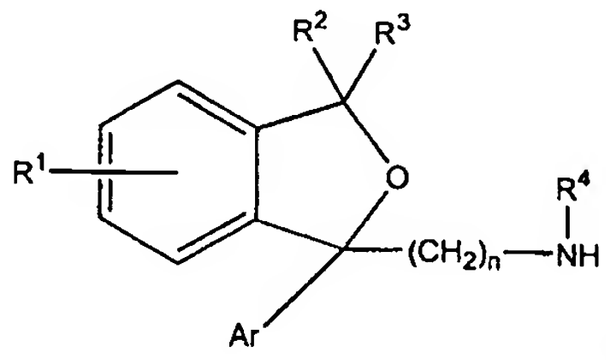
b) alkylating an amine of formula $H-A-(CH_2)_m-B$ wherein A, m and B are as defined above with an alkylating agent of formula



(VI)

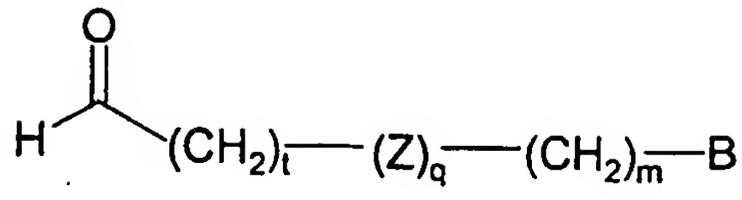
wherein $R^1$, $R^2$, $R^3$, n and Ar are as defined above and G is a suitable leaving group such as halogen, mesylate, or tosylate;

c) reductive alkylation of an amine of formula



(VII)

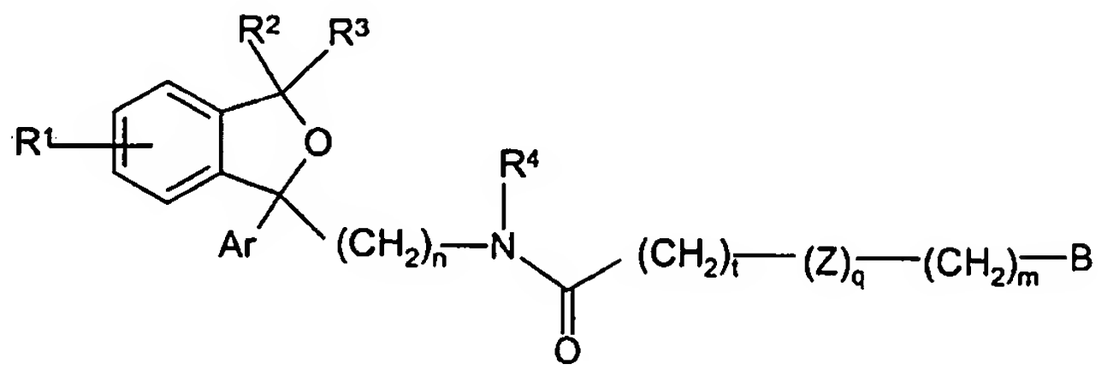
wherein $R^1$, $R^2$, $R^3$, $R^4$, n and Ar are as defined above with an aldehyde of formula



(VIII)

wherein Z, m, q and B are as defined above and t is 1-5;

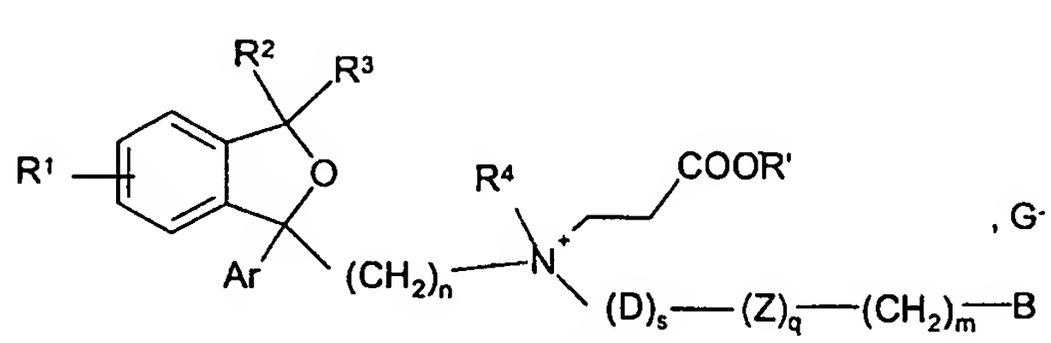
d) reducing an amide of formula



(XI)

wherein $R^1$, $R^2$, $R^3$, $R^4$, n, q, Ar, Z, m and B are as defined above and t is 1-5;

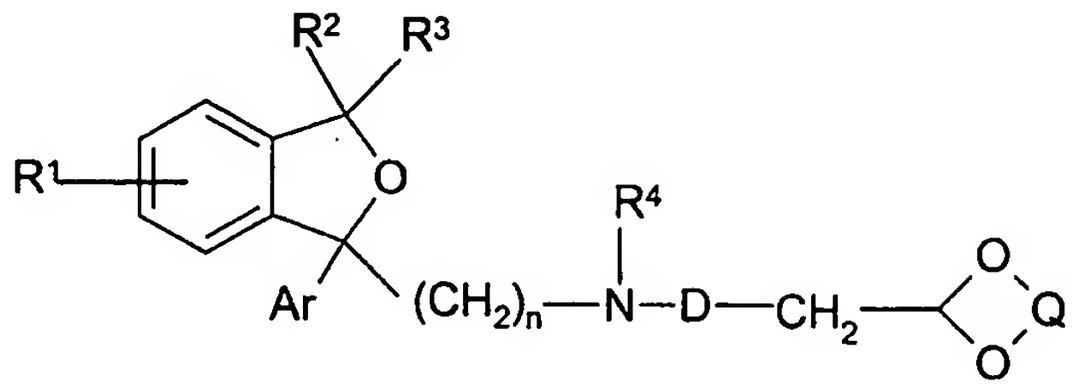
e) releasing final product by the means of Hofmann elimination from a resin of formula



(XII)

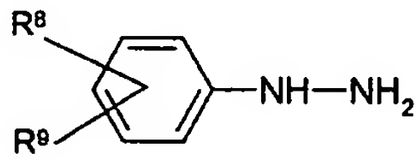
wherein $R^1$, $R^2$, $R^3$, $R^4$, n, s, q, Ar, D, Z, m and B are as defined above, G is as defined above; and HOR' is a hydroxy substituted resin such as cross linked hydroxymethylpolystyrene or Wang resin.

f) reacting a compound of the formula



XIII

wherein $R^1$, $R^2$, $R^3$, $R^4$, Ar, D and N are as defined above; $(OH)_2Q$ is a diol such as substituted ethylene glycol or propylene glycol, or a polymer bound diol, with a hydrazine of formula



XIV

wherein $R^8$ and $R^9$ is as defined above, using Lewis acids as catalyst.

The alkylations according to Methods a and b are generally performed by boiling the reactants under reflux or by heating them at a fixed temperature in a suitable solvent such as acetone, methyl isobutyl ketone, tetrahydrofuran, dioxane, ethanol, 2-propanol, ethyl acetate, N,N-dimethylformamide, dimethyl sulfoxide or 1-methyl-2-pyrrolidinone in the presence of a base such as triethylamine or potassium carbonate. Amines of formula V are prepared by means of demethylation according to the method described by Bigler et al, Eur. J. Med. Chem. Chim. Ther, 1977, 12, 289-295, or by the methods outlined in examples 14 and 15. The starting materials used in example 14 were prepared as described in example 9 or from readily available compounds by standard methods. The enantiomers of 1-[3-(dimethylamino)propyl]-1-(4-fluorophenyl)-1,3-dihydroisobenzofuran-5-carbonitrile used as starting material for the demethylation are prepared as described in EP patent No. 347066. The alkylating agents of formula $G-(D)_s-(Z)_q-(CH_2)_m-B$ are

commercially available, prepared by methods obvious to the chemist skilled in the art or prepared as exemplified in Examples 5-8. Ethyl 1,4-benzodioxan-5-carboxylate used as starting material in Example 5 is prepared by methods obvious to the chemist skilled in the art from the corresponding carboxylic acid prepared according to literature (Fuson et al., J. Org. Chem., 1948, 13, 489). Alkylating agents of formula VI are prepared from the corresponding dimethylamine (Formula VI: G = $N(Me)_2$) as exemplified in example 9. The secondary amines of formula H-A-$(CH_2)_m$-B are commercially available, prepared by methods obvious to the chemist skilled in the art or prepared according to literature procedures. 1-(2-methoxyphenyl)piperazine is prepared according to Pollard et al., J. Org. Chem., 1958, 23, 1333. [2-(2-Methoxyphenoxy)ethyl]methylamine and [2-(3-methoxyphenoxy)ethyl]-methylamine are prepared as exemplified in Examples 7 and 10 using commercially available 2-methoxyphenoxyacetic acid and 3-methoxyphenoxyacetic acid, respectively, as starting materials.

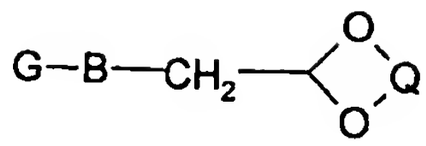
The reductive alkylations according to method c and d are performed according to standard literature methods using $NaCNBH_3$, $NaBH_4$ or $NaBH(OAc)_3$ as reducing agent in a suitable solvent.

The reductions according to Methods e and f are generally performed by use of $LiAlH_4$, $AlH_3$ or diborane in an inert solvent such as tetrahydrofuran, dioxane, or diethyl ether at room temperature or at a slightly elevated temperature.

The release of final products by means of Hofmann elimination in Method g is generally performed by the use of an organic base such as triethylamine or diisopropylethylamine in an aprotic organic solvent such as dichloromethane, toluene or N,N-dimethylformamide. The polymer of formula XII is prepared in a synthesis sequence as exemplified in Example 4 and described in the following. The starting acryl ester resin ($CH_2CHC(O)OR'$) is prepared according to literature procedures (Brown et al., J. Am. Chem. Soc., 1997, 119, 3288-95) by acylation of commercially available hydroxy substituted resins such as cross linked hydroxymethylpolystyrene or Wang resin with acryloyl chloride. Secondary amines of formula $H_2N$-D-Z-$(CH_2)_m$-B are introduced by Michael addition in an organic solvent

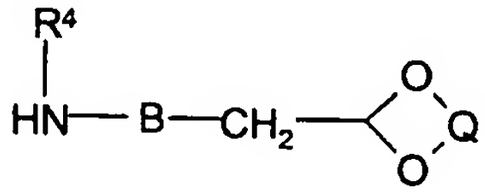
such as N,N-dimethylformamide at ambient temperature. The secondary amines used are either commercially available, prepared by methods obvious to the chemist skilled in the art or prepared according to literature procedures. 3-(2-Methoxyphenyl)propylamine is prepared according to Leeson et al., J. Med. Chem. 1988, 31, 37-54, 3-(3-methoxyphenyl)propylamine according to Meise et al. Liebigs Ann. Chem., 1987, 639-42, 3-(2-methoxyphenoxy)propylamine according to Augsein et al., J. Med. Chem., 1965, 8, 356-67, 3-(3-methoxyphenoxy)propylamine according to Bremner et al., Aust. J. Chem. 1984, 37, 129-41, 2-benzyloxyethylamine according to Harder et al. Chem. Ber. 1964, 97, 510-19, 2-(1*H*-indolyl-3-yl)ethylamine according to Nenitzescu et al., Chem. Ber., 1958, 91, 1141-45 and 3-(1*H*-indolyl-3-yl)propylamine according to Jackson et al., J. Am. Chem. Soc., 1930, 52, 5029. The second diversifying group is introduced by means of alkylation with an agent of formula VI by boiling the reactants under reflux or by heating them at a fixed temperature in a suitable solvent such as tetrahydrofuran, dioxane, ethanol, 2-propanol, ethyl acetate, N,N-dimethylformamide, dimethyl sulfoxide or 1-methyl-2-pyrrolidinone in the presence of a soluble base such as diisopropylethylamine or triethylamine, or by means of reductive alkylation with an aldehyde of formula IX using standard solid phase synthesis literature methods using $NaCNBH_3$, $NaBH_4$ or $NaBH(OAc)_3$ as reducing agent in a suitable solvent. The third diversifying group was introduced by means of quarternisation using an alkylating agent of formula $R^4$-G in an organic solvent such as tetrahydrofuran, dioxane, ethanol, 2-propanol, ethyl acetate, N,N-dimethylformamide, dimethyl sulfoxide or 1-methyl-2-pyrrolidinone at ambient temperature giving resins of formula XII.

The indole formation according to method h is performed by the reaction of acetals of formula XIII with aryl hydrazines of formula XIV resulting in the corresponding hydrazones, which subsequently are converted into indoles by means of the Fischer indole synthesis. The synthesis sequence is preferably performed as a one-pot procedure using a Lewis acid catalysts, preferably zinc chloride or boron fluoride, or protic acids, preferably sulfuric acid or phosphoric acid, in a suitable solvent such as acetic acid or ethanol at an elevated temperature. Acetals of formula XIII are prepared by alkylation of secondary amines of formula V with acetals of formula XV



XV

using the conditions described above for methods a and b. Alternatively, the acetals of formula XIII are prepared by alkylation of acetals of formula XVI



XVI

with an alkylating agent of formula VI using the conditions described above for methods a and b. The acetals of formula XVI are prepared by reaction of acetals of formula XV with primary amines of formula $NH_2R^4$ using standard conditions.

Polymer bound acetals of formula XV is prepared by reaction of aldehydes of formula G-B-$CH_2$CHO with commercially available 2,2-dimethyl-1,3-dioxolan-4-yl-methoxymethyl polystyrene in a suitable solvent such as toluene, using p-toluenesulfonic acid as catalyst at elevated temperature. 4-Chlorobutanal, 5-chloropentanal, and 6-chlorohexanal were prepared in analogy to the method described by Normant et al., Tetrahedron 1994, 50 (40), 11665.

## Examples

Melting points were determined on a Büchi SMP-20 apparatus and are uncorrected. Mass spectra were obtained on a Quattro MS-MS system from VG Biotech, Fisons Instruments. The MS-MS system was connected to an HP 1050 modular HPLC system. A volume of 20-50 µl of the sample (10 µg/ml) dissolved in a mixture of 1% acetic acid in acetonitril/water 1:1 was introduced via the autosampler at a flow of 30 µl/min into the Electrospray Source. Spectra were obtained at two standard sets of operating conditions.

Analytical LC-MS data were obtained on a PE Sciex API 150EX instrument equipped with IonSpray source and Shimadzu LC-8A/SLC-10A LC system. The LC conditions (50 X 4.6

mm YMC ODS-A with 5 µm particle size) were linear gradient elution with water/acetonitrile/trifluoroacetic acid (90:10:0.05) to water/acetonitrile/trifluoroacetic acid (10:90:0.03) in 7 min at 2 mL/min. Purity was determined by integration of the UV trace (254 nm). The retention times $R_t$ are expressed in minutes.

One set to obtain molecular weight information (MH+) (21 eV) and the other set to induce fragmentation patterns (70 eV). The background was subtracted. The relative intensities of the ions are obtained from the fragmentation pattern. When no intensity is indicated for the Molecular Ion (MH+), this ion was only present under the first set of operating conditions. Preparative LC-MS-separation was performed on the same instrument. The LC conditions (50 X 20 mm YMC ODS-A with 5 µm particle size) were linear gradient elution with water/acetonitrile/trifluoroacetic acid (80:20:0.05) to water/acetonitrile/trifluoroacetic acid (10:90:0.03) in 7 min at 22.7 mL/min. Fraction collection was performed by split-flow MS detection.

$^1$H NMR spectra were recorded at 500.13 MHz on a Bruker Avance DRX500 instrument or at 250.13 MHz on a Bruker AC 250 instrument. Deuterated chloroform (99.8%D) or dimethyl sulfoxide (99.9%D) were used as solvents. TMS was used as internal reference standard. Chemical shift values are expressed in ppm-values. The following abbreviations are used for multiplicity of NMR signals: s=singlet, d=doublet, t=triplet, q=quartet, qui=quintet, h=heptet, dd=double doublet, dt=double triplet, dq=double quartet, tt=triplet of triplets, m=multiplet. NMR signals corresponding to acidic protons are generally omitted. Content of water in crystalline compounds was determined by Karl Fischer titration. Standard workup procedures refer to extraction with the indicated organic solvent from proper aqueous solutions, drying of combined organic extracts (anhydrous $MgSO_4$ or $Na_2SO_4$), filtering and evaporation of the solvent *in vacuo*. For column chromatography silica gel of type Kieselgel 60, 230-400 mesh ASTM was used.

**Example 1**

(+)-1-[3-[[4-(1,4-Benzodioxan-5-yl)butyl]methylamino]propyl]-1-(4-fluorophenyl)-1,3-dihydroisobenzofuran-5-carbonitrile (**1a**). A mixture of 5-(4-bromobutyl)-1,4-benzodioxane (1.5 g, 5.5 mmol), (+)-1-[3-(methylamino)propyl]-1-(4-fluorophenyl)-1,3-dihydroisobenzofuran-5-carbonitrile (2.2. g, 5.5 mmol), potassium carbonate (3.0 g, 22

mmol), and methyl isobutyl ketone (150 mL) was boiled under reflux for 16 h. After cooling to room temperature the organic phase was washed with water (150 mL), the solvents evaporated *in vacuo* and the remaining oil purified by column chromatography (ethyl acetate/heptane/triethylamine 75:20:5) affording 2.0 g (73%) of the title compound as an oil: $[\alpha]^{22}_D$ + 8.93° (c 0.5; $CH_3OH$). $^1H$ NMR ($CDCl_3$) δ 1.25-1.35 (m, 1H), 1.40-1.60 (m, 5H), 2.05-2.30 (m, 9H), 2.55 (t, 2H), 4.20-4.30 (m, 4H), 5.10-5.20 (m, 2H), 6.65-6.75 (m, 3H), 7.00 (t, 2H), 7.35 (d,1H), 7.40 (dd, 2H), 7.50 (s, 1H), 7.60 (d, 1H); MS m/z 501 (MH+, 100), 262 (27), 149 (77), 109 (52).

The following compounds were prepared analogously:

(+)-1-[3-[[3-(1,4-Benzodioxan-5-yl)propyl]methylamino]propyl]-1-(4-fluorophenyl)-1,3-dihydroisobenzofuran-5-carbonitrile oxalate (**1b**): mp 114-16°C (ethyl acetate);$[\alpha]^{22}_D$ + 8.96° (c 1.0; $CH_3OH$); $^1H$ NMR (DMSO-*d6*) δ 1.35-1.45 (m, 1H),1.45-1.55 (m, 1H), 1.80 (m, 2H), 2.20-2.30 (m, 2H), 2.45-2.55 (m, 2H), 2.60 (s, 3H), 2.90 (m, 2H), 2.95 (m, 2H), 4.20-4.30 (m, 4H), 5.20 (m, 2H), 6.65-6.75 (m, 3H), 7.10-7.20 (m, 2H), 7.55-7.60 (m, 2H), 7.70-7.80 (m, 1H), 7.80-7.95 (m, 2H); MS m/z 488 (MH+, 100), 262 (33), 149 (52), 109 (55).

1-[3-[[2-(1,4-Benzodioxan-5-yl)ethyl]methylamino]propyl]-1-(4-fluorophenyl)-1,3-dihydroisobenzofuran-5-carbonitrile oxalate (**1c**): mp 118-20°C (ethyl acetate); $^1H$ NMR (DMSO-*d6*) δ 1.40-1.70 (m, 2H), 2.25 (t, 2H), 2.70 (s, 3H), 2.75-2.90 (m, 2H), 2.90-3.15 (m, 4H), 4.15-4.30 (m, 4H), 5.20 (m, 2H), 6.65-6.80 (m, 3H), 7.20 (t, 2H), 7.60 (dd, 2H), 7.70-7.85 (m, 3H); MS m/z 473 (MH+, 64), 323 (13), 262 (24), 163 (100), 109 (25).

1-[3-[[1,4-Benzodioxan-5-ylmethyl]methylamino]propyl]-1-(4-fluorophenyl)-1,3-dihydroisobenzofuran-5-carbonitrile oxalate (**1d**): mp 160-62 °C (acetone/methanol); $^1H$ NMR (DMSO-*d6*) δ 1.40-1.70 (m, 2H), 2.25 (t, 2H), 2.60 (s, 3H), 2.90 (t, 2H), 4.00 (s, 2H), 4.20-4.30 (m, 4H), 5.20 (m, 2H), 6.80-7.00 ( m, 3H), 7.15 (t, 2H), 7.50 – 7.65 (dd, 2H), 7.70-7.85 (m, 3H); MS m/z 459 (MH+, 7), 109 (100).

**Example 2**

1-(4-Fluorophenyl)-1-[3-[4-(2-methoxyphenyl)piperazinyl]propyl]-1,3-dihydroisobenzofuran-5-carbonitrile (**2a**). A mixture of 1-(3-chloropropyl)-1-(4-fluorophenyl)-1,3-dihydroisobenzofuran-5-carbonitrile (2.5 g, 7.9 mmol), 1-(2-methoxyphenyl)piperazine (2.0 g, 10.4 mmol), potassium carbonate (3 g, 22 mmol) and methyl isobutyl ketone (200 mL) was boiled under reflux for 16 h. After cooling to room temperature the organic phase was washed with water (200 mL), the solvents were evaporated *in vacuo* and the remaining oil purified by column chromatography (ethyl acetate/heptane/triethylamine 75:20:5). The title compound crystallised from diethyl ether 1.5 g (40 %): mp 147-49 °C; $^1$H NMR (DMSO-$d_6$) δ 1.30-1.65 (m, 2H), 2.10-2.30 (m, 2H), 2.40 (t, 2H), 2.50-2.70 (m, 4H), 2.90-3.20 (m, 4H), 3.85 (s, 3H), 5.20 (m, 2H), 6.70-7.10 (m, 6H), 7.30-7.55 (m, 4H), 7.60 (d, 1H); MS m/z, 472 (MH+, 100), 262 (14), 109 (19).

The following compounds were prepared analogously:

1-(4-Fluorophenyl)-1-[3-[[2-(2-methoxyphenoxy)ethyl]methylamino]propyl]-1,3-dihydroisobenzofuran-5-carbonitrile (**2b**): (oil) $^1$H NMR ($CDCl_3$) δ 1.30-1.40 (m, 1H), 1.40-1.55 (m, 1H), 2.10-2.20 (m, 2H), 2.25 (s, 3H), 2.40-2.45 (t, 2H), 2.70-2.80 (m, 2H), 3.70 (s, 3H), 4.05 (t, 2H), 5.15 (m, 2H), 6.85-7.00 (m, 6H), 7.30-7.45 (m, 3H), 7.50 (s, 1H), 7.55 (d, 1H).

1-(4-Fluorophenyl)-1-[3-[[2-(3-methoxyphenoxy)ethyl]methylamino]propyl]-1,3-dihydroisobenzofuran-5-carbonitrile (**2c**): (oil) $^1$H NMR ($CDCl_3$) δ 1.30-1.40 (m, 1H), 1.40-1.55 (m, 1H), 2.10-2.20 (m, 2H), 2.25 (s, 3H), 2.40 (t, 2H), 2.70-2.75 (m, 2H), 3.70 (s, 3H), 4.00 (t, 2H), 5.15 (m, 2H), 6.40-6.55 (m, 3H), 7.00 (t, 2H), 7.20 (t, 1H), 7.35 (d, 1H), 7.40 (dd, 2H), 7.50 (s, 1H), 7.55 (d, 1H).

(*S*)-1-[3-[[4-(1*H*-Indol-3-yl)butyl]methylamino]propyl]-1-(4-fluorophenyl)-1,3-dihydro-isobenzofuran-5-carbonitrile (**2d**): LC/MS (m/z) 482 ($MH^+$), Rt = 4.24, purity: 84 %.

1-[3-[[4-(1*H*-Indol-3-yl)butyl]methylamino]propyl]-1-phenyl-1,3-dihydroisobenzofuran (**2e**): LC/MS (m/z) 439 ($MH^+$), Rt = 4.33, purity: 77 %.

(*S*)-1-[3-[[3-(1*H*-Indol-3-yl)propyl]methylamino]propyl]-1-(4-fluorophenyl)-1,3-dihydroisobenzofuran-5-carbonitrile (**2f**): LC/MS (m/z) 468 ($MH^+$), Rt = 4.11, purity: >99 %.

1-[3-[[3-(1*H*-Indol-3-yl)propyl]methylamino]propyl]-1-phenyl-1,3-dihydroisobenzofuran (**2g**): LC/MS (m/z) 425 ($MH^+$), Rt = 4.15, purity: >99 %.

5-[3-[[3-(1-Phenyl-1,3-dihydroisobenzofuran-1-yl)propyl]methylamino]propyl]-1,4-benzodioxane (**2h**): LC/MS (m/z) 444 ($MH^+$), Rt = 4.12, purity: 97 %.

5-[3-[[3-[1-(3-Chlorophenyl)-1,3-dihydroisobenzofuran-1-yl]propyl]methylamino]propyl]-1,4-benzodioxane (**2i**): LC/MS (m/z) 478 ($MH^+$), Rt = 4.45, purity: 93 %.

5-[3-[[3-[1-(4-Fluorophenyl)-1,3-dihydroisobenzofuran-1-yl]propyl]methylamino]propyl]-1,4-benzodioxane (**2j**): LC/MS (m/z) 462 ($MH^+$), Rt = 4.21, purity: 93 %.

5-[3-[[3-[1-(3-Trifluoromethylphenyl)-1,3-dihydroisobenzofuran-1-yl]propyl]methylamino]propyl]-1,4-benzodioxane (**2k**): LC/MS (m/z) 512 ($MH^+$), Rt = 4.59, purity: 90 %.

1-[3-[[3-(1,4-Benzodioxan-5-yl)propyl]methylamino]propyl]-1-(4-chlorophenyl)-1,3-dihydroisobenzofuran-5-carbonitrile (**2l**): LC/MS (m/z) 503 ($MH^+$), Rt = 4.59, purity: >99 %.

1-[3-[4-(1*H*-Indol-4-yl)piperazinyl]propyl]-1-(4-fluorophenyl)-1,3-dihydroisobenzofuran-5-carbonitrile (**2m**): LC/MS (m/z) 481 ($MH^+$), Rt = 5.61, purity: 97 %.

1-[3-[4-(1*H*-Indol-5-yl)piperazinyl]propyl]-1-(4-fluorophenyl)-1,3-dihydroisobenzofuran-5-carbonitrile (**2n**): LC/MS (m/z) 481 ($MH^+$), Rt = 5.69, purity: 94 %.

1-[3-[4-(6-chloro-1*H*-Indol-3-yl)piperidinyl]propyl]-1-(4-fluorophenyl)-1,3-dihydroisobenzofuran-5-carbonitrile (**2o**): LC/MS (m/z) 514 ($MH^+$), Rt = 6.38, purity: 96 %.

**Example 3**

5-[3-[[3-[-5-Fluoro-1-(4-fluorophenyl)-1,3-dihydroisobenzofuran-1-yl]propyl]methylamino]propyl]-1,4-benzodioxane oxalate (**3**). A solution of 3-(1,4-benzodioxan-5-yl)propionic acid (0.8 g, 3.8 mmol), thionyl chloride (1 mL, 13.7 mmol) and one droplet of N,N-dimethylformamide in dichloromethane (30 mL) was boiled under reflux for 2 h. The volatile solvents were evaporated *in vacuo* and the remaining oil was

dissolved in dichloromethane (30 mL). The resulting solution was added to a solution [3-[-5-fluoro-1-(4-fluorophenyl)-1,3-dihydroisobenzofuran-1-yl]propyl]methylamine (3.0 g, 10 mmol) and triethylamine (10 mL) in dichloromethane (100 mL). After stirring for 16 h the volatile solvents were evaporated *in vacuo* and the remaining oil was purified by column chromatography (ethyl acetate/heptane 75:25) affording 1.4 g of crude amide which was used without further purification.

To a solution of the amide (1.4 g, 2.8 mmol) in tetrahydrofuran (200 mL) was added lithium aluminum hydride (1.0 g, 2.6 mmol). After boiling of the resulting mixture under reflux for 3 h, the reaction mixture was cooled to 0 °C and carefully treated with water (1 mL) and 4 N aqueous sodium hydroxide (1 mL). The resulting mixture was filtered and dried ($Na_2SO_4$). Evaporation of the volatile solvents afforded the title compound as an oil which was precipitated as its oxalate in acetone 0.9 g (19%): mp 131-33 °C; $^1$H NMR (DMSO-$d_6$) δ 1.35-1.45 (m, 1H), 1.45-1.55 (m, 1H), 1.75-1.80 (m, 2H), 2.10-2.25 (m, 2H), 2.50-2.55 (m, 2H), 2.60 ( s, 3H), 2.90 (t, 2H), 2.95 (t, 2H), 4.20-4.25 (m, 4H), 5.10 (m, 2H), 6.65-6.75 (m, 3H), 7.10-7.15 (m, 4H), 7.45-7.60 (m, 3H); MS m/z, 480 (MH+, 100), 225 (34), 109 (51).

**Example 4**

1-[3-[[2-(1*H*-Indol-3-yl)ethyl]methylamino]propyl]-1-(4-fluorophenyl)-1,3-dihydroisobenzofuran-5-carbonitrile (**4a**). To a suspension of acryl ester Wang resin ($CH_2CHC(O)OR'$, HOR' = Wang resin) (loading 1.0 mmol/g) (300 mg, 0.30 mmol) (prepared from Wang resin (Loading 1.09 mmol/g, 200-400 mesh, 1% divinylbenzene) in analogy with the procedure described for the preparation of acryl ester hydroxymethyl polystyrene by Brown et al., J. Am. Chem. Soc., 1997, 119, 3288-95) in N,N-dimethylformamide (1.5 mL) was added a solution of 2-(1*H*-indolyl-3-yl)ethylamine (96 mg, 0.60 mmol) in N,N-dimethylformamide (1.5 mL). After stirring of the resulting suspension at room temperature for 16 h, the resin was filtered off and subsequently washed with 0.3 M diisopropylethylamine in N,N-dimethylformamide (3 X 2.5 mL), methanol (2 X 2.5 mL) and dichloromethane (2 X 2.5 mL).

To a suspension of the resulting resin in acetonitrile (1.5 mL) was added a solution of 1-(3-chloropropyl)-1-(4-fluorophenyl)-1,3-dihydroisobenzofuran-5-carbonitrile (**9**)

(473 mg, 1.5 mmol) in acetonitrile (1.5 mL) and diisopropylethylamine (280 mL, 1.6 mmol). After heating of the resulting mixture at 75 °C under stirring for 16 h, the resin was filtered off. The resin was subsequently washed with acetonitrile (3 X 2.5 mL), methanol (3 X 2.5 mL), and dichloromethane (3 X 2.5 mL). The resin was suspended in N,N-dimethylformamide and diisopropylethylamine (280 mL, 1.6 mmol) and acetic anhydride (140 mL, 1.5 mmol) was added. After stirring of the resulting mixture for 16 h the resin was filtered off and washed with N,N-dimethylformamide (3 X 2.5 mL), methanol (3 X 2.5 mL), and dichloromethane (3 X 2.5 mL).

The intermediate resin was suspended in N,N-dimethylformamide (2 mL) and a solution of iodomethan (187 mL, 3.0 mmol) in N,N-dimethylformamide was added. After stirring of the resulting mixture for 16 h at room temperature, the resin was filtered off and washed with N,N-dimethylformamide (3 X 2.5 mL), methanol (3 X 2.5 mL), and dichloromethane (3 X 2.5 mL). To the resulting resin was added N,N-dimethylformamide (3.0 mL) and Di-isopropylethylamine (165 mL, 0.94 mmol) and the mixture was stirred for 16 h. The resin was filtered off and washed with methanol (2 X 2.0 mL). The cleavage solution and the washing solutions were collected and the solvent evaporated *in vacuo*. The remaining oil was purified by ion exchange chromatography using an 6 mL Varian SCX column (1225-6011). The column was preconditioned with 10% acetic acid in methanol (3 mL) and the crude product was loaded on the column in a 2:1 mixture of methanol and 1-methyl-2-pyrrolidinone (3 mL). After the column was washed with methanol (18 mL) and acetonitrile (3 mL) the product was eluted from the column with 4 N ammonia in methanol (4 mL) and subsequent evaporation of the solvents *in vacuo* afforded 13.9 mg (10%) of the title compound as an oil: LC/MS (m/z) 454 ($MH^+$), Rt = 6.13 , purity: 98 %.

The following compounds were prepared analogously:

1-(4-Fluorophenyl)-1-[3-[[2-(3-methoxyphenyl)ethyl]methylamino]propyl]-1,3-dihydroisobenzofuran-5-carbonitrile (**4b**): LC/MS (m/z) 445 ($MH^+$), $R_t$ = 8.58 , purity: 88%

1-(4-Fluorophenyl)-1-[3-[[2-(3-methoxyphenyl)ethyl](prop-2-en-1-yl)amino]propyl]-1,3-dihydroisobenzofuran-5-carbonitrile (**4c**): $^1H$ NMR ($CDCl_3$) δ 1.30-1.60 (m, 2H), 2.00-2.20 (m, 2H), 2.40-2.55 (m, 2H), 2.55-2.70 (m, 4H), 3.00-3.15 (broad s, 2 H), 3.80 (s, 3H), 5.05-

5.20 (m, 4H), 5.75-5.85 (m, 1H), 6.65-6.80 (m, 3H), 7.00 (t, 2H), 7.20 (t, 1H), 7.30 (d, 1H), 7.40 (m, 2H), 7.50 (s, 1H), 7.60 (d, 1H); LC/MS (m/z) 471 ($MH^+$), $R_t$ = 8.85 , purity: 91%

1-(4-Fluorophenyl)-1-[3-[[2-(2-methoxyphenyl)ethyl](prop-2-en-1-yl)amino]propyl]-1,3-dihydroisobenzofuran-5-carbonitrile (**4d**): $^1H$ NMR ($CDCl_3$) δ 1.25-1.40 (m, 1H), 1.40-1.55 (m, 1H), 2.05-2.25 (m, 2H), 2.40-2.50 (m, 2H), 2.50-2.65 (m, 2H), 2.65-2.75 (m, 2H), 3.00-3.15 (m, 2 H), 3.80 (s, 3H); 5.05-5.20 (m, 4H), 5.75-5.90 (m, 1H), 6.75-6.90 (m, 2H), 6.95-7.10 (m, 3H), 7.20 (t, 1H), 7.30 (d, 1H), 7.35-7.45 (m, 2H), 7.45 (s, 1H), 7.60 (d, 1H); LC/MS (m/z) 471 ($MH^+$), $R_t$ = 7.82 , purity: >89%

1-[3-[[2-(2,5-Dimethoxyphenyl)ethyl]methylamino]propyl]-1-(4-fluorophenyl)-1,3-dihydroisobenzofuran-5-carbonitrile (**4e**): LC/MS (m/z) 475 ($MH^+$), $R_t$ = 8.68 , purity: 94%

1-[3-[[2-(2,5-Dimethoxyphenyl)ethyl](prop-2-en-1-yl)amino]propyl]-1-(4-fluorophenyl)-1,3-dihydroisobenzofuran-5-carbonitrile (**4f**): LC/MS (m/z) 500 ($MH^+$), $R_t$ = 8.95 , purity: 90%

1-(4-Fluorophenyl)-1-[3-[[2-phenoxyethyl]methylamino]propyl]-1,3-dihydroisobenzofuran-5-carbonitrile (**4g**): LC/MS (m/z) 431 ($MH^+$), $R_t$ = 8.58 , purity: 95%

1-[3-[[2-(1*H*-Indolyl-3-yl)ethyl](prop-2-en-1-yl)amino]propyl]-1-(4-fluorophenyl)-1,3-dihydroisobenzofuran-5-carbonitrile (**4h**): LC/MS (m/z) 480 ($MH^+$), $R_t$ = 8.87 , purity: 93%

1-(4-Fluorophenyl)-1-[3-[[2-phenoxyethyl](prop-2-en-1-yl)amino]propyl]-1,3-dihydroisobenzofuran-5-carbonitrile (**4i**): LC/MS (m/z) 457 ($MH^+$), $R_t$ = 6.40 , purity:>99%

1-(4-Fluorophenyl)-1-[3-[[3-(2-methoxyphenyl)propyl]methylamino]propyl]-1,3-dihydroisobenzofuran-5-carbonitrile (**4j**): LC/MS (m/z) 459 ($MH^+$), $R_t$ = 6.43 , purity:>99%

1-(4-Fluorophenyl)-1-[3-[[3-(2-methoxyphenyl)propyl](prop-2-en-1-yl)amino]propyl]-1,3-dihydroisobenzofuran-5-carbonitrile (**4k**): LC/MS (m/z) 485 ($MH^+$), $R_t$ = 6.77 , purity: >99%

1-(4-Fluorophenyl)-1-[3-[[3-(3-methoxyphenyl)propyl](prop-2-en-1-yl)amino]propyl]-1,3-dihydroisobenzofuran-5-carbonitrile (**4l**): LC/MS (m/z) 485 ($MH^+$), $R_t$ = 6.63 , purity: >99%

1-(4-Fluorophenyl)-1-[3-[[3-(2-methoxyphenoxy)propyl]methylamino]propyl]-1,3-dihydroisobenzofuran-5-carbonitrile (**4m**): LC/MS (m/z) 475 ($MH^+$), $R_t$ = 6.20 , purity: >99%

1-(4-Fluorophenyl)-1-[3-[[3-(2-methoxyphenoxy)propyl](prop-2-en-1-yl)amino]propyl]-1,3-dihydroisobenzofuran-5-carbonitrile (**4n**): LC/MS (m/z) 501 ($MH^+$), $R_t$ = 6.50 , purity: >99%

1-(4-Fluorophenyl)-1-[3-[[3-(3-methoxyphenoxy)propyl]methylamino]propyl]-1,3-dihydroisobenzofuran-5-carbonitrile (**4o**): LC/MS (m/z) 475 ($MH^+$), $R_t$ = 6.35 , purity: >99%

1-(4-Fluorophenyl)-1-[3-[[3-(3-methoxyphenoxy)propyl](prop-2-en-1-yl)amino]propyl]-1,3-dihydroisobenzofuran-5-carbonitrile (**4p**): LC/MS (m/z) 501 ($MH^+$), $R_t$ = 6.65 , purity: >99%

1-[3-[(2-Benzyloxyethyl)methylamino]propyl]-1-(4-fluorophenyl)-1,3-dihydroisobenzofuran-5-carbonitrile (**4q**): LC/MS (m/z) 445 ($MH^+$), $R_t$ = 6.18 , purity: 98%

1-[3-[(2-Benzyloxyethyl)(prop-2-en-1-yl)amino]propyl]-1-(4-fluorophenyl)-1,3-dihydroisobenzofuran-5-carbonitrile (**4r**): LC/MS (m/z) 471 ($MH^+$), $R_t$ = 6.55 , purity: 97%

1-[3-[[3-(1*H*-Indol-3-yl)propyl]methylamino]propyl]-1-(4-fluorophenyl)-1,3-dihydroisobenzofuran-5-carbonitrile (**4s**): LC/MS (m/z) 468 ($MH^+$), $R_t$ = 6.28 , purity:80%

1-[3-[[3-(1*H*-Indol-3-yl)propyl](prop-2-en-1-yl)amino]propyl]-1-(4-fluorophenyl)-1,3-dihydroisobenzofuran-5-carbonitrile (**4t**): LC/MS (m/z) 494 ($MH^+$), $R_t$ = 6.60 , purity:82%

1-[3-[[3-(1*H*-Indol-3-yl)propyl](prop-2-yn-1-yl)amino]propyl]-1-(4-fluorophenyl)-1,3-dihydroisobenzofuran-5-carbonitrile (**4u**): LC/MS (m/z) 492 ($MH^+$), $R_t$ = 6.59 , purity:73%

**Example 5**

5-hydroxymethyl-1,4-benzodioxan (**5**). To a suspension of lithium aluminum hydride (7.0 g, 0.18 mol) in dry diethyl ether (100 mL) was added a solution of ethyl 1,4-benzodioxan-5-carboxylate (35 g, 0.17 mol) in diethyl ether (100 mL). After boiling under reflux for 2 h, the reaction mixture was cooled to 0 °C and carefully treated with water (35 mL) and 4 N aqueous sodium hydroxide (35 mL). The resulting mixture was filtered and dried ($Na_2SO_4$). Evaporation of the solvents afforded 25 g (88%) crystalline title compound: mp 51-53 °C; $^1$H NMR ($CDCl_3$) δ 2.50 (s, 1H), 4.20-4.3 ( m, 4H), 4.60 (s, 2H), 6.75-6.90 (m, 3H).

**Example 6**

2-(1,4-benzodioxan-5-yl)acetic acid (**6**). To a solution of 5-hydroxymethyl-1,4-benzodioxan (8.0 g, 48 mmol) in dichloromethane (200 mL) was added two droplets of N,N-dimethylformamide and thionyl chloride (5.0 mL, 68 mmol) at room temperature. After the resulting solution was boiled under reflux for 1 h and subsequently cooled to room temperature water (100 mL) was added. The phases were separated and the organic phase was dried ($MgSO_4$) and the solvents evaporated *in vacuo*. A solution of the remaining oil (8.5 g, 46 mmol) was added to a mixture of sodium cyanide (5.0 g, 102 mmol) and N,N-dimethylformamide (100 mL) at room temperature. After stirring for 16 h at room temperature ice was added and the resulting slurry was extracted with diethyl ether (2 X 250 mL). The collected organic phases were washed with saturated calcium chloride, dried ($Na_2SO_4$) and the solvents were evaporated *in vacuo*. A mixture of the remaining oil (6.0 g, 34 mmol), ethanol (200 mL), sodium hydroxide (6.0 g) and water (6 mL) was

boiled under reflux for 16 h. After evaporation of the solvents *in vacuo,* water (200 mL) was added and the resulting slurry was extracted with diethyl ether (2 X 200 mL). The collected organic phases were washed with brine, dried ($Na_2SO_4$) and the solvents were evaporated *in vacuo* affording 4.0 g (43%) of the title compound as an oil: $^1$H NMR ($CDCl_3$) δ 3.65 (s, 2H), 4.15-4.30 (m, 4H), 6.70-6.85 (m, 3H).

**Example 7**

5-(2-bromoethyl)-1,4-benzodioxan (**7a**). To a solution of 2-(1,4-benzodioxan-5-yl)acetic acid (**6**) (4.0 g, 21 mmol) in tetrahydrofuran (200 mL) was added lithium aluminum hydride (1.0 g, 26 mmol). After boiling under reflux for 2 h the reaction mixture was cooled to 0 °C and carefully treated with water (1 mL) and 4 N aqueous sodium hydroxide (1 mL). The resulting mixture was filtered and dried ($Na_2SO_4$). Evaporation of the solvents afforded crude intermediate alcohol (3.9 g, 21 mmol) as an oil which was used without further purification. To a solution of the intermediate alcohol and tetrabromomethane (8.8 g, 27 mmol) in acetonitrile (120 mL) was added triphenylphosphine (6.3 g, 24.9 mmol) in small portions at 0 °C. After reaction for further 15 minutes at 0 °C the solvents were evaporated *in vacuo* and the remaining oil was purified by column chromatography (ethyl acetate/heptane 66:34) affording 5.5 g (99%) of the title compound as an oil: $^1$H NMR ($CDCl_3$) δ 3.15 (t, 2H), 3.55 (t, 2H), 4.20-4.35 (m, 4H), 6.65-6.85 (m, 3H).

The following compounds were prepared analogously:

5-(3-Bromopropyl)-1,4-benzodioxan (**7b**): (oil) $^1$H NMR ($CDCl_3$) δ 2.15 (qui, 2H), 2.75 (t, 2H), 3.40 (t, 2H), 4.20-4.30 (m, 4H), 6.65-6.75 (m, 3H).

5-(4-Bromobutyl)-1,4-benzodioxan (**7c**): (oil) $^1$H NMR ($CDCl_3$) δ 1.70-1.80 (qui, 2H), 1.85-1.90 (qui, 2H), 2.60 (t, 2H), 3.40 (t, 2H), 4.25 (m, 4H), 6.65-6.75 (m, 3H).

1-(2-Bromoethoxy)-2-methoxybenzene (**7d**): (oil) $^1$H NMR ($CDCl_3$) δ 3.65 (t, 2H), 3.85 (s, 3H), 4.30 (t, 2H), 6.80-7.05 (m, 4H).

1-(2-Bromoethoxy)-3-methoxybenzene (**7e**): (oil) $^1$H NMR ($CDCl_3$) δ 3.60 (t, 2H), 3.80 (s, 3H), 4.25 (t, 2H), 6.45-6.55 (m, 3H), 7.15 (t, 1H).

**Example 8**

4-(1,4-Benzodioxan-5-yl)butanoic acid (**8a**). Neat 5-(4-bromoethyl)-1,4-benzodioxan (**7c**) (18.0 g, 74 mmol) was added to a mixture of diethyl malonate (12 g, 75 mmol), potassium tert-butoxide (8.4 g, 75 mmol), toluene (250 mL) and dimethyl sulfoxide (50 mL) at room temperature. The resulting mixture was heated at 50 °C for 3 h, cooled to room temperature and water was added. After the slurry was acidified with concentrated hydrochloric acid the phases were separated. The organic phase was dried ($Na_2SO_4$) and the solvents evaporated *in vacuo*. The remaining oil was dissolved in ethanol (200 mL) and 9 N aqueous sodium hydroxide. After boiling of the resulting mixture under reflux for 15 minutes the solution was stirred at room temperature for 1 h. The solvents were evaporated and the remaining oil was diluted in water (200 mL) and extracted with diethyl ether (2 X 100 mL). The aqueous phase was acidified with 4 N hydrochloric acid and extracted with ethyl acetate (2 X 200 mL). Drying of the collected organic phases and evaporation of the solvents *in vacuo* afforded the intermediate dicarboxylic acid as an oil (5.0 g). The crude oil was diluted in pyridine (10 mL) and the resulting solution was heated at 115 °C for 1 h. After cooling to room temperature, water (50 mL) was added and the aqueous phase was acidified with 4 N hydrochloric acid. The resulting slurry was extracted with diethyl ether (2 X 50 mL) and the collected organic phases were dried ($Na_2SO_4$). Evaporation of the solvents *in vacuo* afforded 3.8 g (23%) of the title compound as an oil.

The following compound was prepared analogously:

3-(1,4-Benzodioxan-5-yl)propionic acid (**8b**): (oil) $^1$H NMR ($CDCl_3$) δ 2.65 (t, 2H), 2.95 (t, 2H), 4.20-4.30 (m, 4H), 6.65-6.80 (m, 3H).

**Example 9**

1-(3-Chloropropyl)-1-(4-fluorophenyl)-1,3-dihydroisobenzofuran-5-carbonitrile (**9**). To a mixture of 1-[3-(methylamino)propyl]-1-(4-fluorophenyl)-1,3-dihydroisobenzofuran-5-carbonitrile (43 g, 138 mmol), potassium carbonate (30 g, 217 mmol), and ethanol (400

mL) was added ethyl bromoacetate (20 mL, 180 mmol) at room temperature and the resulting mixture was boiled under reflux for 90 minutes. After cooling to room temperature water (800 mL) and ethyl acetate (500 mL) was added and the phases were separated. The organic phase was washed with brine, dried ($Na_2SO_4$) and the solvents evaporated *in vacuo*. The remaining oil (36 g, 101 mmol) was added slowly to a mixture of ethyl chloroformate (50 mL, 523 mmol), potassium carbonate (36 g, 260) and toluene (300 mL) at 90 °C. After boiling of the resulting mixture under reflux for 1 h and cooling to room temperature, the solvents were evaporated *in vacuo*. The remaining oil was purified by column chromatography (ethyl acetate/heptane 1:3) giving 15 g (34%) of the title compound as an oil: $^1$H NMR ($CDCl_3$) δ 1.60-1.90 (m, 2H), 2.20-2.45 (m, 2H), 3.45-3.55 (m, 2H), 5.20 (m, 2H), 6.95-7.10 (t, 2H), 7.40-7.55 (m, 4H), 7.60 (d, 1H).

**Example 10**

[2-(2-Methoxyphenoxy)ethyl]methylamine (**10a**). A solution of 1-(2-bromoethoxy)-2-methoxybenzene (**7d**) (7.7 g, 33 mmol) in a 33% solution of methylamine in ethanol was heated at 80 °C in a sealed tube for 16 h. After cooling to room temperature, the solvents were evaporated *in vacuo*. A 2 N aqueous solution of sodium hydroxide was added to the remaining oil and the resulting slurry was extracted with ethyl acetate (2 X 250 mL). The collected organic phases were dried ($Na_2SO_4$) and the solvents evaporated *in vacuo* giving 5.9 g (98%) of the title compound as an oil: $^1$H NMR ($CDCl_3$) δ 1.85 (broad s, 1H), 2.50 (s, 3H), 3.00 (t, 2H), 3.85 (s, 3H), 4.10 (t, 2H), 6.85-6.95 (m, 4H).

The following compound was prepared analogously:

[2-(3-Methoxyphenoxy)ethyl]methylamine (**10b**): (oil) $^1$H NMR ($CDCl_3$) δ 1.85 (broad s, 1H), 2.50 (s, 3H), 2.95 (t, 2H), 3.80 (s, 3H), 4.05 (t, 2H), 6.45-6.55 (m, 3H), 7.15 (t, 1H).

**Example 11**

2-(4-Chlorobutyl)-dioxolan-4-ylmethoxymethyl polystyrene (**11a**). A 2 L round bottom flask was charged with 2,2-dimethyldioxolan-4-ylmethoxymethyl polystyrene (90 g, 72 mmol, commercially available as (±)-1-(2,3-isopropylidene) glycerol polystyrene from Calbiochem-Novabiochem, cat. no. 01-64-0291). Toluene (900 mL) followed by p-

toluenesulfonic acid mono hydrate (5.0 g, 26 mmol), sodium sulfate (25 g), and readily available 5-chloropentanal (25.5 g, 211 mmol) were added and the mixture heated at reflux for 12 h. The reflux condenser was replaced by a Dean-Stark apparatus and the mixture was heated at reflux for an additional 3 h. After cooling of the reaction mixture to 60 °C, the resin was filtered and washed with toluene (200 mL), tetrahydrofuran/pyridine (1:1, 200 mL), tetrahydrofuran/water/pyridine (10:10:1, 200 mL), methanol (200 mL), water (200 mL), tetrahydrofuran (200 mL), dichloromethane (200 mL), methanol (3 X 200 mL), and dichloromethane (3 X 200 mL). The resin was dried *in vacuo* (55 °C, 12 h) to yield the title compound **11a** (97 g).

The following compounds were prepared analogously:

2-(3-Chloropropyl)-dioxolan-4-ylmethoxymethyl polystyrene (**11b**)

2-(5-Chloropentyl)-dioxolan-4-ylmethoxymethyl polystyrene (**11c**)

**Example 12**

1-[3-[[3-(1*H*-Indol-3-yl)propyl]methylamino]propyl]-1-(4-fluorophenyl)-1,3-dihydroisobenzofuran-5-carbonitrile (**4s**). 2-(4-Chlorobutyl)-dioxolan-4-ylmethoxymethyl polystyrene (**11a**) (8.0 g, 6.1 mmol) was suspended in dry N,N-dimethylformamide (90 mL). Sodium iodide (3.38 g, 22.5 mmol) was added followed by diisopropylethylamine (6.30 mL, 36 mmol) and 1-[3-(methylamino)propyl]-1-(4-fluorophenyl)-1,3-dihydroisobenzofuran-5-carbonitrile (5.56 g, 18 mmol). The reaction mixture was heated at 80 °C under stirring for 12 h. After cooling to room temperature, the resin was filtered and washed with with N,N-dimethylformamide (3 X 65 mL), methanol (3 X 60 mL), tetrahydrofuran (3 X 60 mL), and then subsequently with methanol and tetrahydrofuran (each approximately 40 mL, 5 cycles). Finally, the resin was washed with tetrahydrofuran (4 X 40 mL) and dried *in vacuo* (55 °C, 12 h, 9.5 g).

An aliquot of this material (147 mg, 0.112 mmol) and phenylhydrazine hydrochloride (43 mg, 0.297 mmol) were mixed in a reactor tube. A 0.5 M solution of anhydrous zinc chloride in acetic acid (1.5 mL) was added and the reaction tube was sealed. The reaction mixture was stirred for 12 h at 75 °C. After cooling to room temperature, the reaction mixture was filtered and the residual resin washed with dimethylsulfoxide (1.5 mL). To the combined filtrates was added saturated aqueous sodium bicarbonate solution (1.5 mL). The

solution was loaded on a reversed solid phase extraction column (C-18, 1 g, Varian Mega Bond Elut®, Chrompack cat. no. 220508), pre-conditioned with methanol (3 mL) and water (3 mL). The column was washed with water (4 mL) and the product was eluted with methanol (4.5 mL). The resulting solution was loaded on an ion exchange column (SCX, 1 g, Varian Mega Bond Elut®, Chrompack cat. no. 220776), pre-conditioned with 10 % solution of acetic acid in methanol (3 mL) and the column was washed with methanol (4 mL) and acetonitrile (4 mL), followed by elution with 4 N solution of ammonia in methanol (4.5 mL). Evaporation of the volatile solvents afforded the title compound (**4s**) as a colourless oil (22 mg, 42 %). LC/MS (m/z) 468 ($MH^+$), Rt = 4.30, purity: 83 %.

The following compounds were prepared analogously:

1-[3-[[2-(5-Methyl-1*H*-indol-3-yl)ethyl]methylamino]propyl]-1-(4-fluorophenyl)-1,3-dihydroisobenzofuran-5-carbonitrile (**12a**): LC/MS (m/z) 468 ($MH^+$), Rt = 4.22, purity: 96 %.

1-[3-[[2-(7-Fluoro-1*H*-indol-3-yl)ethyl]methylamino]propyl]-1-(4-fluorophenyl)-1,3-dihydroisobenzofuran-5-carbonitrile (**12b**): $^1H$ NMR ($CDCl_3$) δ 1.2-1.4 (m, 1H), 1.4-1.55 (m,1H), 2.0-2.25 (m, 2H), 2.25 (s, 3H), 2.39 (t, 2H), 2.60 (t, 2H), 2.86 (t, 2H), 5.05-5.21 (m, 2H), 6.93-7.07 (m, 4H), 7.17-7.3 (m, 2H), 7.3-7.4 (m, 3H), 7.4-7.5 (m, 1H), 7.5-7.6 (m, 1H); LC/MS (m/z) 472 ($MH^+$), Rt = 4.12, purity: 86 %.

5-Fluoro-1-[3-[[3-(5-methyl–1*H*-indol-3-yl)propyl]methylamino]propyl]-1-(4-fluorophenyl)-1,3-dihydroisobenzofuran (**12c**): LC/MS (m/z) 475 ($MH^+$), Rt = 4.57, purity: 92 %.

5-Fluoro-1-[3-[[3-(7-fluoro-1*H*-indol-3-yl)propyl]methylamino]propyl]-1-(4-fluorophenyl)-1,3-dihydroisobenzofuran (**12d**): LC/MS (m/z) 479 ($MH^+$), Rt = 4.47, purity: 94 %.

1-[3-[[3-(5-Methyl –1*H*-indol-3-yl)propyl]methylamino]propyl]-1-(4-fluorophenyl)-1,3-dihydroisobenzofuran-5-carbonitrile (**12e**): LC/MS (m/z) 482 ($MH^+$), Rt = 4.54, purity: 80 %.

1-[3-[Ethyl[3-(1*H*-indol-3-yl)propyl]amino]propyl]-1-(4-fluorophenyl)-1,3-dihydroisobenzofuran-5-carbonitrile (**12f**): LC/MS (m/z) 482 ($MH^+$), Rt = 4.31, purity: 94 %.

1-[3-[Ethyl[2-(5-methyl –1*H*-indol-3-yl)ethyl]amino]propyl]-1-(4-fluorophenyl)-1,3-dihydroisobenzofuran-5-carbonitrile (**12g**): LC/MS (m/z) 482 ($MH^+$), Rt = 4.38, purity: 89 %.

1-[3-[[3-(7-Fluoro-1*H*-indol-3-yl)propyl]methylamino]propyl]-1-(4-fluorophenyl)-1,3-dihydroisobenzofuran-5-carbonitrile (**12h**): LC/MS (m/z) 486 ($MH^+$), Rt = 4.16, purity: 79 %.

1-[3-[[3-(5-Fluoro-1*H*-indol-3-yl)propyl]methylamino]propyl]-1-(4-fluorophenyl)-1,3-dihydroisobenzofuran-5-carbonitrile (**12i**): $^1H$ NMR ($CDCl_3$) δ 1.23-1.39 (m, 1H), 1.39-1.54 (m, 1H), 1.80 (tt, 2H), 2.06-2.24 (m, 5H), 2.30 (t, 2H), 2.34 (t, 2H), 2.68 (t, 2H), 5.13 (d, 1H), 5.17 (d, 1H), 6.93 (dt, 2H), 6.99 (t, 2H), 7.21 (dd, 1H), 7.23-7.29 (m, 1H), 7.33 (d, 1H), 7.40 (dd, 2H), 7.47 (s, 1H), 7.55 (d, 1H), 8.01 (s, 1H); LC/MS (m/z) 486 ($MH^+$), Rt = 4.12, purity: 98 %.

1-[3-[Ethyl[2-(5-fluoro-1*H*-indol-3-yl)ethyl]amino]propyl]-1-(4-fluorophenyl)-1,3-dihydroisobenzofuran-5-carbonitrile (**12j**): $^1H$ NMR ($CDCl_3$) δ 1.02 (t, 3H), 1.25-1.38 (m, 1H), 1.42-1.54 (m, 1H), 2.10 (ddd, 1H), 2.18 (ddd, 1H), 2.49 (t, 2H), 2.56 (q, 2H), 2.61-2.70 (m, 2H), 2.74-2.82 (m, 2H), 5.13 (d, 1H), 5.18 (d, 1H), 6.94 (dt, 2H), 6.99 (t, 2H), 7.19 (dd, 1H), 7.23-7.30 (m, 2H), 7.38 (dd, 2H), 7.47 (s, 1H), 7.54 (d, 1H), 8.01 (s, 1H); LC/MS (m/z) 486 ($MH^+$), Rt = 4.24, purity: 95 %.

1-[3-[Ethyl[2-(7-fluoro-1*H*-indol-3-yl)ethyl]amino]propyl]-1-(4-fluorophenyl)-1,3-dihydroisobenzofuran-5-carbonitrile (**12k**): $^1H$ NMR ($CDCl_3$) δ 1.02 (t, 3H), 1.22-1.37 (m, 1H), 1.42-1.53 (m,1H), 2.0-2.2 (m, 2H), 2.36-2.6 (m, 4H), 2.67 (t, 2H), 2.81 (t, 2H), 5.12 (dd, 1H), 5.16 (d, 1H), 6.86-7.06 (m, 4H), 7.2-7.4 (m, 5H), 7.46 (d, 1H), 7.54 (d, 1H); LC/MS (m/z) 486 ($MH^+$), Rt = 4.26, purity: 91 %.

1-[3-[[2-(5-Chloro-1*H*-indol-3-yl)ethyl]methylamino]propyl]-1-(4-fluorophenyl)-1,3-dihydroisobenzofuran-5-carbonitrile (**12l**): LC/MS (m/z) 488 ($MH^+$), Rt = 4.30, purity: 85 %.

1-[3-[[3-(5-Chloro-1*H*-indol-3-yl)propyl]methylamino]propyl] – 5-fluoro –1-(4-fluorophenyl) –1,3-dihydroisobenzofuran (**12m**): LC/MS (m/z) 495 ($MH^+$), Rt = 4.64, purity: 94 %.

1-[3-[[4-(5-Methyl–1*H*-indol-3-yl)butyl]methylamino]propyl]-1-(4-fluorophenyl)-1,3-dihydroisobenzofuran-5-carbonitrile (**12n**): LC/MS (m/z) 496 ($MH^+$), Rt = 4.50, purity: 78 %.

1-[3-[Ethyl[3-(5-methyl–1*H*-indol-3-yl)propyl]amino]propyl]-1-(4-fluorophenyl)-1,3-dihydroisobenzofuran-5-carbonitrile (**12o**): LC/MS (m/z) 496 ($MH^+$), Rt = 4.50, purity: 92 %.

1-[3-[Ethyl[3-(7-fluoro–1*H*-indol-3-yl)propyl]amino]propyl]-1-(4-fluorophenyl)-1,3-dihydroisobenzofuran-5-carbonitrile (**12p**): LC/MS (m/z) 500 ($MH^+$), Rt = 4.39, purity: 91 %.

1-[3-[Ethyl[3-(5-fluoro–1*H*-indol-3-yl)propyl]amino]propyl]-1-(4-fluorophenyl)-1,3-dihydroisobenzofuran-5-carbonitrile (**12q**): $^1H$ NMR ($CDCl_3$) δ 0.95 (t, 3H), 1.21-1.36 (m, 1H), 1.36-1.50 (m, 1H), 1.77 (tt, 2H), 2.10 (ddd, 1H), 2.18 (ddd, 1H), 2.34-2.50 (m, 6H), 2.65 (t, 2H), 5.12 (d, 1H), 5.15 (d, 1H), 6.90-7.04 (m, 4H), 7.20 (dd, 1H), 7.25 (dd, 1H), 7.30 (d, 1H), 7.36 (m, 2H), 7.45 (s, 1H), 7.52 (d, 1H), 8.12 (s, 1H); LC/MS (m/z) 500 ($MH^+$), Rt = 4.35, purity: 94 %.

1-[3-[[3-(5-Chloro-1*H*-indol-3-yl)propyl]methylamino]propyl]-1-(4-fluorophenyl)-1,3-dihydroisobenzofuran-5-carbonitrile (**12r**): LC/MS (m/z) 502 ($MH^+$), Rt = 4.55, purity: 91 %.

1-[3-[[2-(7-Chloro –1*H*-indol-3-yl)ethyl]ethylamino]propyl]-1-(4-fluorophenyl)-1,3-dihydroisobenzofuran-5-carbonitrile (**12s**): LC/MS (m/z) 502 ($MH^+$), Rt = 4.41, purity: 80 %.

1-[3-[[2-(5-Chloro-1*H*-indol-3-yl)ethyl]ethylamino]propyl]-1-(4-fluorophenyl)-1,3-dihydroisobenzofuran-5-carbonitrile (**12t**): LC/MS (m/z) 502 ($MH^+$), Rt = 4.44, purity: 95 %.

1-[3-[[2-(5,7-Difluoro –1*H*-indol-3-yl)ethyl]ethylamino]propyl]-1-(4-fluorophenyl)-1,3-dihydroisobenzofuran-5-carbonitrile (**12u**): LC/MS (m/z) 504 ($MH^+$), Rt = 4.35, purity: 92 %.

1-[3-[[4-(5-Fluoro –1*H*-indol-3-yl)butyl]ethylamino]propyl]-1-(4-fluorophenyl)-1,3-dihydroisobenzofuran-5-carbonitrile (**12v**): LC/MS (m/z) 514 ($MH^+$), Rt = 4.50, purity: 91 %.

1-[3-[[4-(5-Chloro –1*H*-indol-3-yl)butyl]methylamino]propyl]-1-(4-fluorophenyl)-1,3-dihydroisobenzofuran-5-carbonitrile (**12w**): LC/MS (m/z) 516 ($MH^+$), Rt = 4.59, purity: 90 %.

1-[3-[[3-(5-Chloro-1*H*-indol-3-yl)propyl]ethylamino]propyl]-1-(4-fluorophenyl)-1,3-dihydroisobenzofuran-5-carbonitrile (**12x**): LC/MS (m/z) 516 ($MH^+$), Rt = 4.56, purity: 97 %.

1-[3-[[3-(5,7-Difluoro –1*H*-indol-3-yl)propyl]ethylamino]propyl]-1-(4-fluorophenyl)-1,3-dihydroisobenzofuran-5-carbonitrile (**12y**): LC/MS (m/z) 518 ($MH^+$), Rt = 4.47, purity: 90 %.

1-[3-[[2-(5-Bromo –1*H*-indol-3-yl)ethyl]methylamino]propyl]-1-(4-fluorophenyl)-1,3-dihydroisobenzofuran-5-carbonitrile (**12z**): LC/MS (m/z) 532 ($MH^+$), Rt = 4.46, purity: 87 %.

1-[3-[[3-(5-Bromo –1*H*-indol-3-yl)propyl]methylamino]propyl]-1-(4-fluorophenyl)-1,3-dihydroisobenzofuran-5-carbonitrile (**12aa**): LC/MS (m/z) 546 ($MH^+$), Rt = 4.59, purity: 88 %.

1-[3-[[2-(5-Bromo –1*H*-indol-3-yl)ethyl]ethylamino]propyl]-1-(4-fluorophenyl)-1,3-dihydroisobenzofuran-5-carbonitrile (**12ab**): LC/MS (m/z) 546 ($MH^+$), Rt = 4.50, purity: 90 %.

1-[3-[[4-(5-Bromo –1*H*-indol-3-yl)butyl]methylamino]propyl]-1-(4-fluorophenyl)-1,3-dihydroisobenzofuran-5-carbonitrile (**12ac**): LC/MS (m/z) 560 ($MH^+$), Rt = 4.61, purity: 90 %.

1-[3-[[3-(5-Bromo –1*H*-indol-3-yl)propyl]ethylamino]propyl]-1-(4-fluorophenyl)-1,3-dihydroisobenzofuran-5-carbonitrile (**12ad**): LC/MS (m/z) 560 ($MH^+$), Rt = 4.62, purity: 92 %.

1-[3-[Ethyl[2-(5-iodo –1*H*-indol-3-yl)ethyl]amino]propyl]-1-(4-fluorophenyl)-1,3-dihydroisobenzofuran-5-carbonitrile (**12ae**): LC/MS (m/z) 594 ($MH^+$), Rt = 4.60, purity: 82 %.

1-[3-[Ethyl[3-(5-iodo –1*H*-indol-3-yl)propyl]amino]propyl]-1-(4-fluorophenyl)-1,3-dihydroisobenzofuran-5-carbonitrile (**12af**): LC/MS (m/z) 608 ($MH^+$), Rt = 4.72, purity: 71 %.

1-[2-[[4-(5-Chloro –1*H*-indol-3-yl)butyl]methylamino]ethyl]-1-(4-fluorophenyl)-1,3-dihydroisobenzofuran-5-carbonitrile (**12ag**): LC/MS (m/z) 502 ($MH^+$), Rt = 4.50, purity: 90 %.

1-[2-[[4-(5-Bromo –1*H*-indol-3-yl)butyl]methylamino]ethyl]-1-(4-fluorophenyl)-1,3-dihydroisobenzofuran-5-carbonitrile (**12ah**): LC/MS (m/z) 546 ($MH^+$), Rt = 4.55, purity: 83 %.

1-[4-[[2-(5,7-Difluoro –1*H*-indol-3-yl)ethyl]methylamino]butyl]-1-(4-fluorophenyl)-1,3-dihydroisobenzofuran-5-carbonitrile (**12ai**): LC/MS (m/z) 504 ($MH^+$), Rt = 4.36, purity: 87 %.

1-[4-[[2-(7-Chloro –1*H*-indol-3-yl)ethyl]methylamino]butyl]-1-(4-fluorophenyl)-1,3-dihydroisobenzofuran-5-carbonitrile (**12aj**): LC/MS (m/z) 502 ($MH^+$), Rt = 4.42, purity: 70 %.

1-[4-[[2-(5-Chloro –1*H*-indol-3-yl)ethyl]methylamino]butyl]-1-(4-fluorophenyl)-1,3-dihydroisobenzofuran-5-carbonitrile (**12ak**): LC/MS (m/z) 502 ($MH^+$), Rt = 4.45, purity: 91 %.

1-[4-[[2-(5-Bromo –1*H*-indol-3-yl)ethyl]methylamino]butyl]-1-(4-fluorophenyl)-1,3-dihydroisobenzofuran-5-carbonitrile (**12al**): LC/MS (m/z) 546 ($MH^+$), Rt = 4.48, purity: 90 %.

1-[4-[[2-(5-Methyl –1*H*-indol-3-yl)ethyl]methylamino]butyl]-1-(4-fluorophenyl)-1,3-dihydroisobenzofuran-5-carbonitrile (**12am**): LC/MS (m/z) 482 ($MH^+$), Rt = 4.37, purity: 87 %.

1-[4-[[2-(5-Iodo –1*H*-indol-3-yl)ethyl]methylamino]butyl]-1-(4-fluorophenyl)-1,3-dihydroisobenzofuran-5-carbonitrile (**12an**): LC/MS (m/z) 594 ($MH^+$), Rt = 4.57, purity: 83 %.

1-[4-[[2-(5-(2-methyl-2-propyl)–1*H*-indol-3-yl)ethyl]methylamino]butyl]-1-(4-fluorophenyl)-1,3-dihydroisobenzofuran-5-carbonitrile (**12ao**): LC/MS (m/z) 524 ($MH^+$), Rt = 4.85, purity: 91 %.

1-[4-[[2-(5-(2-Propyl) –1*H*-indol-3-yl)ethyl]methylamino]butyl]-1-(4-fluorophenyl)-1,3-dihydroisobenzofuran-5-carbonitrile (**12ap**): LC/MS (m/z) 510 ($MH^+$), Rt = 4.72, purity: 92 %.

**Example 13**

1-[3-[[2-(5-Methyl –1*H*-indol-3-yl)ethyl](prop-2-en-1-yl)amino]propyl]-1-(4-fluorophenyl)-1,3-dihydroisobenzofuran-5-carbonitrile (**13a**).

2-(3-Chloropropyl)-1,3-dioxolan-4-ylmethoxymethyl polystyrene (2.0 g, 1.6 mmol) was suspended in dry N,N-dimethylformamide (15 mL). Sodium iodide (0.67 g, 4.5 mmol) was added followed by diisopropylethylamine (1.70 mL, 9.6 mmol) and allyl amine (0.28 g, 4.8 mmol). The reaction mixture was heated at 80 °C under stirring for 12 h. After cooling to room temperature, the resin was filtered and washed with N,N-dimethylformamide (3 X 15 mL), methanol (3 X 15 mL), tetrahydrofuran (3 X 15 mL), and subsequently with methanol and tetrahydrofuran (each 10 mL, 5 cycles). Finally, the resin was washed with tetrahydrofuran (4 X 10 mL) and dried *in vacuo* (55 °C, 12 h). The resin was then suspended in dry N,N-dimethylformamide (20 mL). Sodium iodide (0.60 g, 4.0 mmol) was added followed by diisopropylethylamine (0.48 mL, 2.7 mmol) and 1-(3-chloropropyl)-1-(4-fluorophenyl)-1,3-dihydroisobenzofuran-5-carbonitrile (**9**) (0.79 g, 2.5 mmol). The reaction mixture was stirred for 12 h at 80 °C. After cooling to room temperature, the resin was filtered and washed with with N,N-dimethylformamide (3 X 15 mL), methanol (3 X 15 mL), tetrahydrofuran (3 X 15 mL), and then subsequently with methanol and tetrahydrofuran (each ca. 15 mL, 5 cycles). Finally, the resin was washed with tetrahydrofuran (4 X 15 mL) and dried *in vacuo* (55 °C, 12 h, 2.1 g).

An aliquot of this material (120 mg, ca. 0.08 mmol) and 4-methylphenylhydrazine hydrochloride (ca. 40 mg, 0.20 mmol) were mixed in a reactor tube. A 0.5 M solution of anhydrous zinc chloride in acetic acid (1.5 mL) was added and the reaction tube was sealed. The reaction mixture was stirred for 12 h at 75 °C. After cooling to room temperature, the reaction mixture was filtered and the residual resin washed with dimethylsulfoxide (1.5 mL). To the combined filtrates was added saturated aqueous sodium bicarbonate solution (1.5 mL). The solution was loaded on a reversed phase column (C-18, 1 g, Varian Mega Bond Elut®, Chrompack cat. no. 220508), pre-conditioned with methanol (3 mL) and water (3 mL). The column was washed with water

(4 mL) and the product was eluted with methanol (4.5 mL). After evaporation of the volatile solvents, the crude product was purified by preparative reversed phase HPLC chromatography. The resulting solution was loaded on an ion exchange column (SCX, 1 g, Varian Mega Bond Elut®, Chrompack cat. no. 220776), pre-conditioned with 10 % solution of acetic acid in methanol (3 mL) and the column was washed with methanol (4 mL) and acetonitrile (4 mL), followed by elution with 4 N solution of ammonia in methanol (4.5 mL). Evaporation of the volatile solvents afforded the title compound (**13a**) as a colorless oil (2 mg, 4 μmol, 5 %). LC/MS (m/z) 494 ($MH^+$), Rt = 4.44, purity: 93 %.

The following compounds were prepared analogously:

1-[3-[[2-(5-Fluoro –1*H*-indol-3-yl)ethyl](prop-2-en-1-yl)amino]propyl]-1-(4-fluorophenyl)-1,3-dihydroisobenzofuran-5-carbonitrile (**13b**): LC/MS (m/z) 498 ($MH^+$), Rt = 4.31, purity: 96 %.

1-[3-[[2-(7-Fluoro –1*H*-indol-3-yl)ethyl](prop-2-en-1-yl)amino]propyl]-1-(4-fluorophenyl)-1,3-dihydroisobenzofuran-5-carbonitrile (**13c**): LC/MS (m/z) 498 ($MH^+$), Rt = 4.34, purity: 86 %.

1-[3-[[3-(5-Fluoro –1*H*-indol-3-yl)propyl](prop-2-en-1-yl)amino]propyl]-1-(4-fluorophenyl)-1,3-dihydroisobenzofuran-5-carbonitrile (**13d**): LC/MS (m/z) 512 ($MH^+$), Rt = 4.48, purity: 96 %.

1-[3-[[3-(7-Fluoro –1*H*-indol-3-yl)propyl](prop-2-en-1-yl)amino]propyl]-1-(4-fluorophenyl)-1,3-dihydroisobenzofuran-5-carbonitrile (**13e**): LC/MS (m/z) 512 ($MH^+$), Rt = 4.49, purity: 78 %.

1-[3-[[2-(5-Chloro –1*H*-indol-3-yl)ethyl](prop-2-en-1-yl)amino]propyl]-1-(4-fluorophenyl)-1,3-dihydroisobenzofuran-5-carbonitrile (**13f**): LC/MS (m/z) 514 ($MH^+$), Rt = 4.52, purity: 86 %.

1-[3-[[2-(5,7-Difluoro –1*H*-indol-3-yl)ethyl]propylamino]propyl]-1-(4-fluorophenyl)-1,3-dihydroisobenzofuran-5-carbonitrile (**13g**): LC/MS (m/z) 518 ($MH^+$), Rt = 4.47, purity: 89 %.

1-[3-[[2-[5-(2-Propyl)-1*H*-indol-3-yl]ethyl](2-propyl)amino]propyl]-1-(4-fluorophenyl)-1,3-dihydroisobenzofuran-5-carbonitrile (**13h**): LC/MS (m/z) 524 ($MH^+$), Rt = 4.78, purity: 96 %.

1-[3-[[3-(4-Fluoro-7-methyl-1*H*-indol-3-yl)propyl](prop-2-en-1-yl)amino]propyl]-1-(4-fluorophenyl)-1,3-dihydroisobenzofuran-5-carbonitrile (**13i**): LC/MS (m/z) 526 ($MH^+$), Rt = 4.65, purity: 83 %.

1-[3-[[2-(4-Chloro-7-methyl-1*H*-indol-3-yl)ethyl](prop-2-en-1-yl)amino]propyl]-1-(4-fluorophenyl)-1,3-dihydroisobenzofuran-5-carbonitrile (**13j**): LC/MS (m/z) 528 ($MH^+$), Rt = 4.67, purity: 79 %.

1-[3-[[3-(5-Chloro –1*H*-indol-3-yl)propyl](prop-2-en-1-yl)amino]propyl]-1-(4-fluorophenyl)-1,3-dihydroisobenzofuran-5-carbonitrile (**13k**): LC/MS (m/z) 528 ($MH^+$), Rt = 4.63, purity: 78 %.

1-[3-[[2-(5-Pyrrolo[3,2-*h*]-1*H*-quinolin-3-yl)ethyl](prop-2-en-1-yl)amino]propyl]-1-(4-fluorophenyl)-1,3-dihydroisobenzofuran-5-carbonitrile (**13l**): LC/MS (m/z) 531 ($MH^+$), Rt = 3.43, purity: 91 %.

1-[3-[[3-(7-Fluoro –1*H*-indol-3-yl)propyl](2-furylmethyl)amino]propyl]-1-(4-fluorophenyl)-1,3-dihydroisobenzofuran-5-carbonitrile (**13m**): LC/MS (m/z) 552 ($MH^+$), Rt = 4.58, purity: 82 %.

1-[3-[[4-(7-Carboxy-1*H*-indol-3-yl)butyl](prop-2-en-1-yl)amino]propyl]-1-(4-fluorophenyl)-1,3-dihydroisobenzofuran-5-carbonitrile (**13n**): LC/MS (m/z) 552 ($MH^+$), Rt = 4.17, purity: 69 %.

1-[3-[[2-[5-Bromo-1*H*-indol-3-yl]ethyl]-propylamino]propyl]-1-(4-fluorophenyl)-1,3-dihydroisobenzofuran-5-carbonitrile (**13o**): LC/MS (m/z) 560 ($MH^+$), Rt = 4.62, purity: 96 %.

1-[3-[[3-(1*H*-Indol-3-yl)propyl](2-phenoxyethyl)amino]propyl]-1-(4-fluorophenyl)-1,3-dihydroisobenzofuran-5-carbonitrile (**13p**): LC/MS (m/z) 574 ($MH^+$), Rt = 4.78, purity: 93 %.

1-[3-[[2-(5-Methyl-1*H*-indol-3-yl)ethyl](2-phenoxyethyl)amino]propyl]-1-(4-fluorophenyl)-1,3-dihydroisobenzofuran-5-carbonitrile (**13q**): LC/MS (m/z) 574 ($MH^+$), Rt = 4.82, purity: 93 %.

1-[3-[[2-(5-Fluoro-1*H*-indol-3-yl)ethyl](2-phenoxyethyl)amino]propyl]-1-(4-fluorophenyl)-1,3-dihydroisobenzofuran-5-carbonitrile (**13r**): LC/MS (m/z) 578 ($MH^+$), Rt = 4.71, purity: 95 %.

1-[3-[[3-(1*H*-Pyrrolo[3,2-*h*]quinolin-3-yl)propyl](2-furylmethyl)amino]propyl]-1-(4-fluorophenyl)-1,3-dihydroisobenzofuran-5-carbonitrile (**13s**): LC/MS (m/z) 585 ($MH^+$), Rt = 3.60, purity: 90 %.

1-[3-[[3-(5-Methyl-1*H*-indol-3-yl)propyl](2-phenoxyethyl)amino]propyl]-1-(4-fluorophenyl)-1,3-dihydroisobenzofuran-5-carbonitrile (**13t**): LC/MS (m/z) 588 ($MH^+$), Rt = 4.96, purity: 82 %.

1-[3-[[3-(5-Fluoro-1*H*-indol-3-yl)propyl](2-phenoxyethyl)amino]propyl]-1-(4-fluorophenyl)-1,3-dihydroisobenzofuran-5-carbonitrile (**13u**): LC/MS (m/z) 592 ($MH^+$), Rt = 4.82, purity: 90 %.

1-[3-[[2-(5,7-Difluoro-1*H*-indol-3-yl)ethyl](2-phenoxyethyl)amino]propyl]-1-(4-fluorophenyl)-1,3-dihydroisobenzofuran-5-carbonitrile (**13v**): LC/MS (m/z) 596 ($MH^+$), Rt = 4.84, purity: 92 %.

1-[3-[[4-(1*H*-Pyrrolo[3,2-*h*]quinolin-3-yl)butyl](2-furylmethyl)amino]propyl]-1-(4-fluorophenyl)-1,3-dihydroisobenzofuran-5-carbonitrile (**13w**): LC/MS (m/z) 599 ($MH^+$), Rt = 3.71, purity: 83 %.

1-[3-[(2-Phenoxyethyl)[2-[5-(2-propyl)-1*H*-indol-3-yl]ethyl]amino]propyl]-1-(4-fluorophenyl)-1,3-dihydroisobenzofuran-5-carbonitrile (**13x**): LC/MS (m/z) 602 ($MH^+$), Rt = 5.24, purity: 78 %.

1-[3-[[2-(5-Bromo-1*H*-indol-3-yl)ethyl](2-phenoxyethyl)amino]propyl]-1-(4-fluorophenyl)-1,3-dihydroisobenzofuran-5-carbonitrile (**13y**): LC/MS (m/z) 638 ($MH^+$), Rt = 4.98, purity: 91 %.

**Example 14**

1-(3-Iodopropyl)-1-(4-fluorophenyl)-1,3-dihydroisobenzofuran-5-carbonitrile (**14a**). A solution/suspension of 1-(3-chloropropyl)-1-(4-fluorophenyl)-1,3-dihydroisobenzofuran-5-carbonitrile (20 g, 35 mmol, 80 % pure) and sodium iodide (285 g, 1.9 mol) in dry acetone (200 ml) was heated at reflux for 24 h. The mixture was evaporated, and partitioned between ether and water. The ether layer was separated, and was washed successively with water and brine. The organic extract was dried over anhydrous magnesium sulfate, filtered and evaporated to give 1-(3-iodopropyl)-1-(4-fluorophenyl)-1,3-dihydroisobenzofuran-5-carbonitrile (25,8 g, 99 %, 80 % pure) as a thick oil. $^1H$ NMR ($CDCl_3$) δ 1.6-1.9 (m, 2H),

2.21 (ddd, 1H), 2.31 (ddd, 1H), 3.16 (td, 2H), 5.12 (dt, 1H), 5.21 (dt, 1H), 7.02 (t, 2H), 7.41 (d, 2H), 7.43 (d, 1H), 7.51 (s, 1H), 7.62 (dq, 1H)

The following compounds were prepared analogously:

1-(2-Iodoethyl)-1-(4-fluorophenyl)-1,3-dihydroisobenzofuran-5-carbonitrile (**14b**): yellow oil, $^1$H NMR ($CDCl_3$) δ 2.4-2.9 (m, 2H), 3.38 (dt, 1H), 3.46 (dt, 1H), 5.15 (d, 1H), 5.21 (d, 1H), 7.03 (t, 2H), 7.35-7.48 (m, 3H), 7.52 (s, 1H), 7.62 (d, 1H).

1-(4-Iodobutyl)-1-(4-fluorophenyl)-1,3-dihydroisobenzofuran-5-carbonitrile (**14c**): yellow oil, $^1$H NMR ($CDCl_3$) δ 1.1-1.5 (m, 2H), 1.81 (tt, 2H), 2.00-2.30 (m, 2H), 3.11 (t, 2H), 5.14 (d, 1H), 5.20 (d, 1H), 7.01 (t, 2H), 7.35-7.47 (m, 3H), 7.51 (s, 1H), 7.60 (d, 1H).

**Example 15**

1-(3-(Ethylamino)propyl)-1-(4-fluorophenyl)-1,3-dihydroisobenzofuran-5-carbonitrile (**15a**). To a stirred solution of 1-(3-iodopropyl)-1-(4-fluorophenyl)-1,3-dihydroisobenzofuran-5-carbonitrile (12.9 g, 30 mmol, 8 % pure) in ethanol (150 mL) was added a solution of ethylamine (20.3 g, 450 mmol) in THF (50 mL) portionwise, and the mixture was stirred over night. The solution was evaporated, and was dissolved/suspended in water. The pH was adjusted to 12 using aqueous sodium hydroxide solution (2 M) and was extracted with ether. The organic extract was washed with brine, dried over anhydrous magnesium sulfate, filtered and evaporated to give an oil. This oil was purified by silica chromatography using 50% v/v ethyl acetate/heptane as eluent, followed by 10% v/v triethylamine/ 40% v/v ethyl acetate/heptane followed by 20% v/v triethylamine/ethyl acetate to give the title compound (5.52 g, 57%) as a pale yellow oil. $^1$H NMR ($CDCl_3$) δ 1.05 (t, 3 H), 1.2-1.6 (m, 2H), 2.15 (ddd, 1H), 2.24 (ddd, 1H), 2.57 (q, 2H) 2.58 (t, 2H), 5.12 (dt, 1H), 5.20 (dt, 1H), 7.00 (t, 2H), 7.38 (d, 1H), 7.42 (dd, 2H), 7.49 (s, 1H), 7.58 (ddt, 1H).

The following compounds were prepared analogously:

1-(2-(Methylamino)ethyl)-1-(4-fluorophenyl)-1,3-dihydroisobenzofuran-5-carbonitrile (**15b**): yellow oil; $^1$H NMR ($CDCl_3$) δ 2.38 (s, 3H), 2.33-2.72 (m, 4H), 5.13 (d, 1H), 5.20 (d, 1H), 7.01 (t, 2H), 7.37-7.47 (m, 3H), 7.50 (s, 1H), 7.59 (d, 1H).

1-(4-(Methylamino)butyl)-1-(4-fluorophenyl)-1,3-dihydroisobenzofuran-5-carbonitrile (**15c**): yellow oil; $^1$H NMR ($CDCl_3$) δ 1.00-1.45 (m, 2H), 1.46 (tt, 2H), 2.10 (ddd, 1H), 2.21 (ddd, 1H), 2.37 (s, 3H), 2.50 (t, 2H), 5.13 (d, 1H), 5.19 (d, 1H), 7.00 (t, 2H), 7.34-7.46 (m, 3H), 7.49 (s, 1H), 7.59 (d, 1H).

**Pharmacological Testing**

The affinity of the compounds of the invention to 5-$HT_{1A}$ receptors was determined by measuring the inhibition of binding of a radioactive ligand at 5-$HT_{1A}$ receptors as described in the following test:

**Inhibition of $^3$H-5-CT Binding to Human 5-$HT_{1A}$ Receptors**

By this method the inhibition by drugs of the binding of the 5-$HT_{1A}$ agonist $^3$H-5-carboxamido tryptamine ($^3$H-5-CT) to cloned human 5-$HT_{1A}$ receptors stably expressed in transfected HeLa cells (HA7) (Fargin, A. *et al*, *J. Biol. Chem.*, **1989**, *264*, 14848) is determined *in vitro*. The assay was performed as a modification of the method described by Harrington, M.A. *et al*, *J. Pharmacol. Exp. Ther.*, **1994**, *268*, 1098. Human 5-$HT_{1A}$ receptors (40 µg of cell homogenate) were incubated for 15 minutes at 37 °C in 50 mM Tris buffer at pH 7.7 in the presence of $^3$H-5-CT. Non-specific binding was determined by including 10 µM of metergoline. The reaction was terminated by rapid filtration through Unifilter GF/B filters on a Tomtec Cell Harvester. Filters were counted in a Packard Top Counter. The results obtained are presented in table 1 below.

The compounds of the invention have also been tested for their effect on re-uptake of serotonin in the following test:

**Inhibition of $^3$H-5-HT Uptake Into Rat Brain Synaptosomes**

Using this method, the ability of drugs to inhibit the accumulation of $^3$H-5-HT into whole rat brain synaptosomes is determined *in vitro*. The assay was performed as described by Hyttel, J., *Psychopharmacology* **1978**, *60*, 13. The results obtained are presented in table 1:

**Table 1**

| Compound No. | Inhibition of $^3$H-5-CT binding $IC_{50}$ ( nM) % inhibition at 100 nM | Inhibition of serotonin reuptake $IC_{50}$ ( nM) % inhibition at 100 nM |
|---|---|---|
| **1a** | 39 | 60 |
| **1b** | 12 | 13 |
| **1c** | 53 | 85 |
| **2a** | 1.0 | 340 |
| **2b** | 6.4 | 40 |
| **2e** | 38 | 15 |
| **2f** | 8.6 | 14 |
| **2g** | 40 | 20 |
| **2j** | 41 | 9.7 |
| **2m** | 4.7 | Not tested |
| **2n** | 15 | Not tested |
| **2o** | 12 | 31 |
| **4a** | 23 | 54 |
| **4b** | 63 | 59% inh. at 100 nM |
| **4c** | 11 | 4% inh. at 100 nM |
| **4d** | 4.5 | 7% inh. at 100 nM |

| | | |
|---|---|---|
| **4e** | 17 | 160 |
| **4f** | 1.6 | 4% inh. at 100 nM |
| **4g** | 18 | 28% inh. at 100 nM |
| **4h** | 3.2 | 69 |
| **4i** | 1.9 | 26% inh. at 100 nM |
| **4j** | 6.1 | 78 |
| **4k** | 0.42 | 100 |
| **4l** | 76% inh. at 100 nM | 27% inh. at 100 nM |
| **4m** | 65% inh. at 100 nM | 74% inh. at 100 nM |
| **4n** | 14 | 39% inh. at 100 nM |
| **4o** | 26 | 73 |
| **4p** | 19 | 6% inh. at 100 nM |
| **4q** | 16 | 60% inh. at 100 nM |
| **4r** | 11 | 19% inh. at 100 nM |
| **4s** | 30 | 35 |
| **4t** | 69% inh. at 100 nM | 73% inh. at 100 nM |
| **4u** | 58% inh. at 100 nM | 44% inh. at 100 nM |
| **12b** | 43 | 10 |
| **12c** | 19 | 17 |
| **12d** | 31 | 12 |
| **12f** | 4.7 | 13 |
| **12i** | 27 | 20 |
| **12j** | 7.9 | 14 |
| **12k** | 3.6 | 8.4 |
| **12o** | 6.2 | 49% inh. at 100 nM |
| **12p** | 19 | 11 |

| | | |
|---|---|---|
| **12q** | 12 | 6.3 |
| **12r** | 16 | 47% inh. at 100 nM |
| **12s** | 7.7 | 18 |
| **12u** | 9.0 | 22 |
| **12v** | 39 | 12 |
| **12x** | 14 | 50% inh. at 100 nM |
| **12aa** | 16 | 37% inh. at 100 nM |
| **12ab** | 20 | 50% inh. at 100 nM |
| **12ad** | 21 | 35% inh. at 100 nM |
| **12ae** | 11 | 49% inh. at 100 nM |
| **12af** | 31 | 38% inh. at 100 nM |
| **13b** | 7.4 | 44 |
| **13c** | 9.6 | 12 |
| **13d** | 15 | 21 |
| **13e** | 22 | 27 |
| **13f** | 31 | 16% inh. at 100 nM |
| **13g** | 18 | 49% inh. at 100 nM |
| **13j** | 16 | 61% inh. at 100 nM |
| **13k** | 19 | Not tested |
| **13p** | 23 | Not tested |
| **13q** | 12 | Not tested |
| **13r** | 8.9 | Not tested |
| **13t** | 23 | Not tested |
| **13u** | 22 | Not tested |
| **13v** | 23 | Not tested |
| **13x** | 26 | Not tested |
| **Pindolol*** | 100 | |
| **Paroxetine*** | - | 0.29 |

Table 1 * reference compounds

Furthermore, the 5-$HT_{1A}$ antagonistic activity of some of the compounds of the invention has been estimated *in vitro* at cloned 5-$HT_{1A}$ receptors stably expressed in transfected HeLa cells (HA7). In this test, 5-$HT_{1A}$ antagonistic activity is estimated by measuring the ability of the compounds to antagonize the 5-HT induced inhibition of forskolin induced cAMP accumulation. The assay was performed as a modification of the method described by Pauwels, P.J. *et al, Biochem. Pharmacol.* **1993**, *45*, 375.

As seen from the above, the compounds of the invention show affinity for the 5-$HT_{1A}$ receptor. Furthermore, many of the compounds of the present invention possess valuable activity as serotonin re-uptake inhibitors.

Accordingly, the compounds are considered useful for the treatment of psychiatric and neurological disorders as mentioned previously.

**Pharmaceutical formulation**

The pharmaceutical formulations of the invention may be prepared by conventional methods in the art. For example: Tablets may be prepared by mixing the active ingredient with ordinary adjuvants and/or diluents and subsequently compressing the mixture in a conventional tabletting machine. Examples of adjuvants or diluents comprise: corn starch, potato starch, talcum, magnesium stearate, gelatine, lactose, gums, and the like. Any other adjuvants or additives usually used for such purposes such as colourings, flavourings, preservatives etc. may be used provided that they are compatible with the active ingredients.

Solutions for injections may be prepared by dissolving the active ingredient and possible additives in a part of the solvent for injection, preferably sterile water, adjusting the solution to desired volume, sterilisation of the solution and filling in suitable ampules or vials. Any suitable additive conventionally used in the art may be added, such as tonicity agents, preservatives, antioxidants, etc.

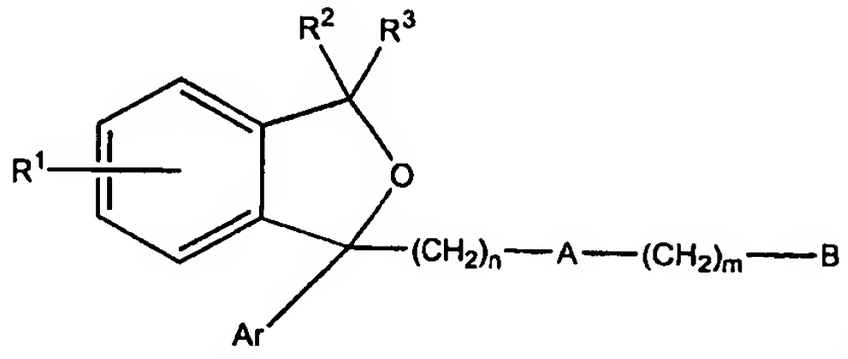
The pharmaceutical compositions of this invention or those which are manufactured in accordance with this invention may be administered by any suitable route, for example orally in the form of tablets, capsules, powders, syrups, etc., or parenterally in the form of

solutions for injection. For preparing such compositions, methods well known in the art may be used, and any pharmaceutically acceptable carriers, diluents, excipients, or other additives normally used in the art may be used.

Conveniently, the compounds of the invention are administered in unit dosage form containing said compounds in an amount of about 0.01 to 1000 mg. The total daily dose is usually in the range of about 0.05 - 500 mg, and most preferably about 0.1 to 50 mg of the active compound of the invention.

**Claims:**

1. An isobenzofuran having the general Formula I:



(I)

wherein

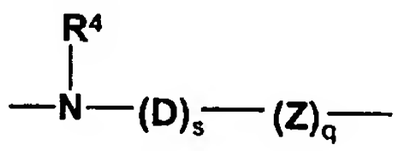
$R^1$ is hydrogen, halogen, trifluoromethyl, trifluoromethylsulfonyloxy, $C_{1-6}$ alkyl, $C_{2-6}$ alkenyl, $C_{2-6}$ alkynyl, $C_{3-8}$ cycloalkyl, $C_{1-6}$ alkoxy, hydroxy, formyl, acyl, amino, $C_{1-6}$ alkylamino, $C_{2-12}$ dialkylamino, acylamino, $C_{1-6}$ alkoxycarbonylamino, aminocarbonylamino, $C_{1-6}$ alkylaminocarbonylamino, $C_{2-12}$ dialkylaminocarbonylamino, nitro, cyano, COOH, or COO-$C_{1-6}$ alkyl;

$R^2$ and $R^3$ are each independently selected from hydrogen, trifluoromethyl, $C_{1-6}$ alkyl, $C_{2-6}$ alkenyl, $C_{2-6}$ alkynyl, $C_{3-8}$ cycloalkyl and $C_{1-6}$ alkoxy;

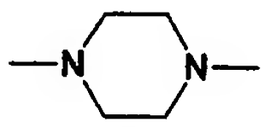
n is 1, 2, 3, 4 or 5;

m is 0 or 1;

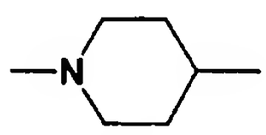
A is selected from the following groups:



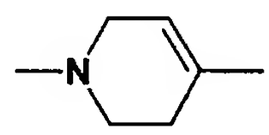
(1)



(2)



(3)



(4)

wherein

Z is O or S;

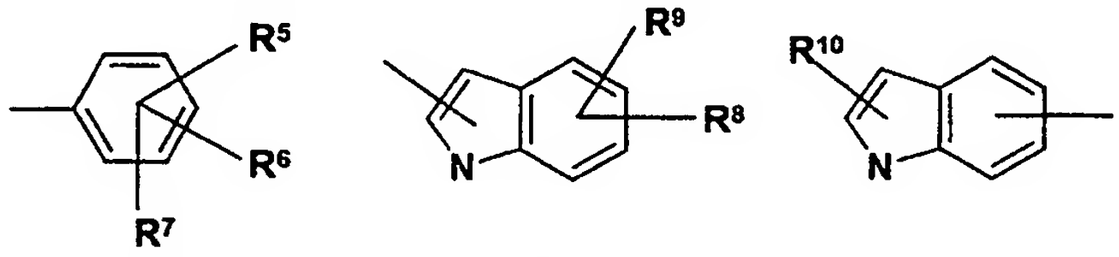
s is 0 or 1;

q is 0 or 1;

$R^4$ is hydrogen, $C_{1-6}$-alkyl, $C_{2-6}$-alkenyl, $C_{2-6}$-alkynyl, $C_{1-6}$-alkyl-Aryl, or $C_{1-6}$-alkyl-O-Aryl;

D is a spacer group selected from branched or straight chain $C_{1-6}$-alkylene, $C_{2-6}$-alkenylene and $C_{2-6}$-alkynylene;

B is a group selected from a group of formula (II), (III), and (IV)




(II) (III) (IV)

wherein $R^5$, $R^6$, $R^7$, $R^8$, $R^9$ and $R^{10}$ are each independently selected among the $R^1$ substituents;

or $R^8$ and $R^9$ together form a fused 5- or 6-membered ring optionally containing further heteroatoms; and the resulting heterocycle is optionally substituted with substituents selected among the $R^1$ substituents;

or two of the groups of $R^5$, $R^6$ and $R^7$ are linked together thereby forming a $—O—(CH_2)_p—O—$ -bridge wherein p is 1 or 2;

Ar and Aryl are independently selected from the group consisting of phenyl, 2–thienyl, 3–thienyl, 2–furanyl, 3–furanyl, 2–pyrimidyl, 1–indolyl, 2–indolyl, 3–indolyl, 1–indol-2-onyl, 3–indol-2-onyl, 2- or 3–benzofuranyl, 2- or 3–benzothiophenyl, 1–naphthyl or 2–naphthyl, each optionally substituted with halogen, $C_{1-6}$ alkyl, $C_{1-6}$ alkoxy, $C_{1-6}$ alkylthio, hydroxy, $C_{1-6}$ alkylsulfonyl, cyano, trifluoromethyl, trifluoromethylsulfonyloxy, $C_{3-8}$ cycloalkyl, $C_{3-8}$ cycloalkyl–$C_{1-6}$ alkyl, nitro, amino, $C_{1-6}$ alkylamino, $C_{2-12}$ dialkylamino, acylamino or alkylenedioxy;

its enantiomers, and pharmaceutically acceptable acid addition salt thereof.

2. A compound of Claim 1, **characterised in** that A is a group of formula (1).

3. A compound of Claim 1, **characterised in** that A is a group of formula (2).

4. A compound of Claim 1, **characterised in** that A is a group of formula (3).

5. A compound of Claim 1, **characterised in** that A is a group of formula (4).

6. A compound of Claim 2, **characterised in** that $R^4$ is methyl, ethyl, propyl, 2-propen-1-yl, 2-furylmethyl, 2-phenoxyethyl;

7. A compound of any of the Claims 2 and 6, **characterised in** that q = 0;

8. A compound of any of the Claims 2 and 6, **characterised in** that q = 1 and Z is O.

9. A compound of any of the Claims 1 - 8, **characterised in** that B is a group of formula (II).

10. A compound of any of the Claims 1 - 8, **characterised in** that B is a group of formula (III).

11. A compound of any of the Claims 1 - 8, **characterised in** that B is a group of formula (IV).

12. A compound of Claim 9, **characterised in** that at least one of $R^5$, $R^6$ and $R^7$, is methoxy.

13. A compound of Claim 9, **characterised in** that Formula (II) is a benzodioxan group or a 1,2-methylenedioxybenzene group.

14. A compound of Claim 10, **characterised in** that Formula (III) is a 3-indolyl.

15. A compound of Claim 14, **characterised in** that the 3-indolyl is substituted in 5-position by methyl, fluoro, chloro, bromo, iodo, *t*-butyl or *i*-propyl, or in 7-position by fluoro, chloro or carboxy; or disubstituted by 5,7-difluoro, 4-fluoro-7-methyl or 4-chloro-7-methyl or the two substituents together form a pyridyl ring fused to the 3-indolyl.

16. A compound of Claim 11, **characterised in** that Formula (IV) is a 4-indolyl or a 5-indolyl group.

17. A compound of any of the Claims 1 - 16, **characterised in** that Ar is phenyl or phenyl substituted with halogen or $CF_3$;

18. A compound of Claim 17, **characterised in** that Ar is phenyl which may be substituted with Cl or F in the 4-position or Cl or $CF_3$ in the 3-position.

19. A compound of any of the Claims 1 - 18, **characterised in** that $R^1$ is H, CN or F in the 5-position of the isobenzofuran group.

20. A compound of any of the Claims 1 - 19, **characterised in** that $R^2$ and $R^3$ are selected from hydrogen or methyl.

21. A compound of any of the Claims 1 - 20, **characterised in** that n = 2, 3 or 4.

22. A compound of claim 21, **characterised in** that n = 3;

23. A compound of any of the Claims 1 - 22, **characterised in** that m = 0.

24. A compound of any of the Claims 1, 18, 19, 20, 21, 22 and 23, **characterised in** that $R^2$ and $R^3$ are both hydrogen; $R^1$ is H, CN or F in the 5-position of the isobenzofuran group; and Ar is phenyl which may be substituted with F or Cl in the 4-position or with Cl or $CF_3$ in the 3-position.

25. A compound of any of the Claims 1 and 24, **characterised in** that A is a group of formula (1); q = 0; $R^4$ is methyl; D is propylene; m = 0; and B is a 1,4-benzodioxan group of Formula (II) attached in the 5-position.

26. A compound of any of the Claims 1 and 24, **characterised in** that A is a group of formula (1); $R^4$ is $CH_3$ or prop-2-en-1-yl; n = 3; D is ethylene or propylene; and B is a phenyl group wherein at least one substituent is OMe.

27. A compound of any of the Claims 1 and 24, **characterised in** that A is a group of formula (1); q is 0; $R^4$ is methyl, ethyl, propyl, 2-propen-1-yl, 2-furylmethyl or 2-phenoxyethyl; D is ethylene or propylene; m = 0; and B is a 3-indolyl group of Formula (III).

28. A compound according to claim 27, **characterised in** that the 3-indolyl group is substituted by methyl, fluoro, chloro, bromo, iodo, *t*-butyl or *i*-propyl in the 5-position; or fluoro, chloro or carboxy in the 7-position; or by 5,7-difluoro, 4-fluoro-7-methyl or 4-chloro-7-methyl; or the two substituents together form a pyridyl ring fused to the 3-indolyl-group.

29. A compound of any of the Claims 1 and 24, **characterised in** that A is a group of formula (2) or (3); n = 3; m = 0; and B is an 4- or 5-indolyl-group of Formula (IV) wherein $R^{10}$ is hydrogen; $R^1$ is CN in the 5-position of the isobenzofuran and Ar is 4-Fluorophenyl.

30. The compound according to claim 1 which is

(-)-1-[3-[[4-(1,4-Benzodioxan-5-yl)butyl]methylamino]propyl]-1-(4-fluorophenyl)-1,3-dihydroisobenzofuran-5-carbonitrile,

1-[3-[[3-(1,4-Benzodioxan-5-yl)propyl]methylamino]propyl]-1-(4-fluorophenyl)-1,3-dihydroisobenzofuran-5-carbonitrile oxalate,

1-[3-[[2-(1,4-Benzodioxan-5-yl)ethyl]methylamino]propyl]-1-(4-fluorophenyl)-1,3-dihydroisobenzofuran-5-carbonitrile oxalate,

1-[3-[[1,4-Benzodioxan-5-ylmethyl]methylamino]propyl]-1-(4-fluorophenyl)-1,3-dihydroisobenzofuran-5-carbonitrile oxalate,

1-(4-Fluorophenyl)-1-[3-[4-(2-methoxyphenyl)piperazinyl]propyl]-1,3-dihydroisobenzofuran-5-carbonitrile,

1-(4-Fluorophenyl)-1-[3-[methyl[2-(2-methoxyphenoxy)ethyl]amino]propyl]-1,3-dihydroisobenzofuran-5-carbonitrile,

1-(4-Fluorophenyl)-1-[3-[methyl[2-(3-methoxyphenoxy)ethyl]amino]propyl]-1,3-dihydroisobenzofuran-5-carbonitrile,

(*S*)-1-[3-[[4-(1*H*-Indol-3-yl)butyl]methylamino]propyl]-1-(4-fluorophenyl)-1,3-dihydroisobenzofuran-5-carbonitrile,

1-[3-[[4-(1*H*-Indol-3-yl)butyl]methylamino]propyl]-1-phenyl-1,3-dihydroisobenzofuran,

(*S*)-1-[3-[[3-(1*H*-Indol-3-yl)propyl]methylamino]propyl]-1-(4-fluorophenyl)-1,3-dihydroisobenzofuran-5-carbonitrile,

1-[3-[[3-(1*H*-Indol-3-yl)propyl]methylamino]propyl]-1-phenyl-1,3-dihydroisobenzofuran,

5-[3-[[3-(1-Phenyl-1,3-dihydroisobenzofuran-1-yl)propyl]methylamino]propyl]-1,4-benzodioxane,

5-[3-[[3-[1-(3-Chlorophenyl)-1,3-dihydroisobenzofuran-1-yl]propyl]methylamino]propyl]-1,4-benzodioxane,

5-[3-[[3-[1-(4-Fluorophenyl)-1,3-dihydroisobenzofuran-1-yl]propyl]methylamino]propyl]-1,4-benzodioxane,

5-[3-[[3-[1-(3-Trifluoromethylphenyl)-1,3-dihydroisobenzofuran-1-yl]propyl]methylamino]propyl]-1,4-benzodioxane,

1-[3-[[3-(1,4-Benzodioxan-5-yl)propyl]methylamino]propyl]-1-(4-chlorophenyl)-1,3-dihydroisobenzofuran-5-carbonitrile,

1-[3-[4-(1*H*-Indol-4-yl)piperazinyl]propyl]-1-(4-fluorophenyl)-1,3-dihydroisobenzofuran-5-carbonitrile,

1-[3-[4-(1*H*-Indol-5-yl)piperazinyl]propyl]-1-(4-fluorophenyl)-1,3-dihydroisobenzofuran-5-carbonitrile,

1-[3-[4-(1*H*-Indol-3-yl)piperidinyl]propyl]-1-(4-fluorophenyl)-1,3-dihydroisobenzofuran-5-carbonitrile,

5-[3-[[3-[-5-Fluoro-1-(4-fluorophenyl)-1,3-dihydroisobenzofuran-1-yl]propyl]methylamino]propyl]-1,4-benzodioxane,

1-[3-[[2-(1*H*-Indolyl-3-yl)ethyl]methylamino]propyl]-1-(4-fluorophenyl)-1,3-dihydroisobenzofuran-5-carbonitrile,

1-(4-Fluorophenyl)-1-[3-[[2-(3-methoxyphenyl)ethyl]methylamino]propyl]-1,3-dihydroisobenzofuran-5-carbonitrile,

1-(4-Fluorophenyl)-1-[3-[[2-(3-methoxyphenyl)ethyl](prop-2-en-1-yl)amino]propyl]-1,3-dihydroisobenzofuran-5-carbonitrile,

1-(4-Fluorophenyl)-1-[3-[[2-(2-methoxyphenyl)ethyl](prop-2-en-1-yl)amino]propyl]-1,3-dihydroisobenzofuran-5-carbonitrile,

1-[3-[[2-(2,5-Dimethoxyphenyl)ethyl]methylamino]propyl]-1-(4-fluorophenyl)- 1,3-dihydroisobenzofuran-5-carbonitrile,

1-[3-[[2-(2,5-Dimethoxyphenyl)ethyl](prop-2-en-1-yl)amino]propyl]-1-(4-fluorophenyl)-1,3-dihydroisobenzofuran-5-carbonitrile,

1-(4-Fluorophenyl)-1-[3-[[2-phenoxyethyl]methylamino]propyl]-1,3-dihydroisobenzofuran-5-carbonitrile,

1-[3-[[2-(1*H*-Indolyl-3-yl)ethyl](prop-2-en-1-yl)amino]propyl]-1-(4-fluorophenyl)-1,3-dihydroisobenzofuran-5-carbonitrile,

1-(4-Fluorophenyl)-1-[3-[[2-phenoxyethyl](prop-2-en-1-yl)amino]propyl]-1,3-dihydroisobenzofuran-5-carbonitrile,

1-(4-Fluorophenyl)-1-[3-[[3-(2-methoxyphenyl)propyl]methylamino]propyl]-1,3-dihydroisobenzofuran-5-carbonitrile,

1-(4-Fluorophenyl)-1-[3-[[3-(2-methoxyphenyl)propyl](prop-2-en-1-yl)amino]propyl]-1,3-dihydroisobenzofuran-5-carbonitrile,

1-(4-Fluorophenyl)-1-[3-[[3-(3-methoxyphenyl)propyl](prop-2-en-1-yl)amino]propyl]-1,3-dihydroisobenzofuran-5-carbonitrile,

1-(4-Fluorophenyl)-1-[3-[[3-(2-methoxyphenoxy)propyl]methylamino]propyl]-1,3-dihydroisobenzofuran-5-carbonitrile,

1-(4-Fluorophenyl)-1-[3-[[3-(2-methoxyphenoxy)propyl](prop-2-en-1-yl)amino]propyl]-1,3-dihydroisobenzofuran-5-carbonitrile,

1-(4-Fluorophenyl)-1-[3-[[3-(3-methoxyphenoxy)propyl]methylamino]propyl]-1,3-dihydroisobenzofuran-5-carbonitrile,

1-(4-Fluorophenyl)-1-[3-[[3-(3-methoxyphenoxy)propyl](prop-2-en-1-yl)amino]propyl]-1,3-dihydroisobenzofuran-5-carbonitrile,

1-[3-[(2-Benzyloxyethyl)methylamino]propyl]-1-(4-fluorophenyl)-1,3-dihydroisobenzofuran-5-carbonitrile,

1-[3-[(2-Benzyloxyethyl)(prop-2-en-1-yl)amino]propyl]-1-(4-fluorophenyl)-1,3-dihydroisobenzofuran-5-carbonitrile,

1-[3-[[3-(1*H*-Indolyl-3-yl)propyl](prop-2-en-1-yl)amino]propyl]-1-(4-fluorophenyl)-1,3-dihydroisobenzofuran-5-carbonitrile,

1-[3-[[3-(1*H*-Indolyl-3-yl)propyl](2-propynyl)amino]propyl]-1-(4-fluorophenyl)-1,3-dihydroisobenzofuran-5-carbonitrile,

1-[3-[[3-(1*H*-Indolyl-3-yl)propyl]methylamino]propyl]-1-(4-fluorophenyl)-1,3-dihydroisobenzofuran-5-carbonitrile,

1-[3-[[2-(5-Methyl-1*H*-indol-3-yl)ethyl]methylamino]propyl]-1-(4-fluorophenyl)-1,3-dihydroisobenzofuran-5-carbonitrile,

1-[3-[[2-(7-Fluoro-1*H*-indol-3-yl)ethyl]methylamino]propyl]-1-(4-fluorophenyl)-1,3-dihydroisobenzofuran-5-carbonitrile,

5-Fluoro-1-[3-[[3-(5-methyl -1*H*-indol-3-yl)propyl]methylamino]propyl]-1-(4-fluorophenyl)-1,3-dihydroisobenzofuran,

5-Fluoro-1-[3-[[3-(7-fluoro-1*H*-indol-3-yl)propyl]methylamino]propyl]-1-(4-fluorophenyl)-1,3-dihydroisobenzofuran,

1-[3-[[3-(5-Methyl -1*H*-indol-3-yl)propyl]methylamino]propyl]-1-(4-fluorophenyl)-1,3-dihydroisobenzofuran-5-carbonitrile,

1-[3-[Ethyl[3-(1*H*-indol-3-yl)propyl]amino]propyl]-1-(4-fluorophenyl)-1,3-dihydroisobenzofuran-5-carbonitrile,

1-[3-[Ethyl[2-(5-methyl -1*H*-indol-3-yl)ethyl]amino]propyl]-1-(4-fluorophenyl)-1,3-dihydroisobenzofuran-5-carbonitrile,

1-[3-[[3-(7-Fluoro-1*H*-indol-3-yl)propyl]methylamino]propyl]-1-(4-fluorophenyl)-1,3-dihydroisobenzofuran-5-carbonitrile,

1-[3-[[3-(5-Fluoro-1*H*-indol-3-yl)propyl]methylamino]propyl]-1-(4-fluorophenyl)-1,3-dihydroisobenzofuran-5-carbonitrile,

1-[3-[Ethyl[2-(5-fluoro-1*H*-indol-3-yl)ethyl]amino]propyl]-1-(4-fluorophenyl)-1,3-dihydroisobenzofuran-5-carbonitrile,

1-[3-[Ethyl[2-(7-fluoro-1*H*-indol-3-yl)ethyl]amino]propyl]-1-(4-fluorophenyl)-1,3-dihydroisobenzofuran-5-carbonitrile,

1-[3-[[2-(5-Chloro-1*H*-indol-3-yl)ethyl]methylamino]propyl]-1-(4-fluorophenyl)-1,3-dihydroisobenzofuran-5-carbonitrile,

1-[3-[[3-(5-Chloro-1*H*-indol-3-yl)propyl]methylamino]propyl] - 5-fluoro -1-(4-fluorophenyl) -1,3-dihydroisobenzofuran,

1-[3-[[4-(5-Methyl -1*H*-indol-3-yl)butyl]methylamino]propyl]-1-(4-fluorophenyl)-1,3-dihydroisobenzofuran-5-carbonitrile,

1-[3-[Ethyl[3-(5-methyl -1*H*-indol-3-yl)propyl]amino]propyl]-1-(4-fluorophenyl)-1,3-dihydroisobenzofuran-5-carbonitrile,

1-[3-[Ethyl[3-(7-fluoro -1*H*-indol-3-yl)propyl]amino]propyl]-1-(4-fluorophenyl)-1,3-dihydroisobenzofuran-5-carbonitrile,

1-[3-[Ethyl[3-(5-fluoro -1*H*-indol-3-yl)propyl]amino]propyl]-1-(4-fluorophenyl)-1,3-dihydroisobenzofuran-5-carbonitrile,

1-[3-[[3-(5-Chloro-1*H*-indol-3-yl)propyl]methylamino]propyl]-1-(4-fluorophenyl)-1,3-dihydroisobenzofuran-5-carbonitrile,

1-[3-[[2-(7-Chloro -1*H*-indol-3-yl)ethyl]ethylamino]propyl]-1-(4-fluorophenyl)-1,3-dihydroisobenzofuran-5-carbonitrile,

1-[3-[[2-(5-Chloro-1*H*-indol-3-yl)ethyl]ethylamino]propyl]-1-(4-fluorophenyl)-1,3-dihydroisobenzofuran-5-carbonitrile,

1-[3-[[2-(5,7-Difluoro -1*H*-indol-3-yl)ethyl]ethylamino]propyl]-1-(4-fluorophenyl)-1,3-dihydroisobenzofuran-5-carbonitrile,

1-[3-[[4-(5-Fluoro -1*H*-indol-3-yl)butyl]ethylamino]propyl]-1-(4-fluorophenyl)-1,3-dihydroisobenzofuran-5-carbonitrile,

1-[3-[[4-(5-Chloro -1*H*-indol-3-yl)butyl]methylamino]propyl]-1-(4-fluorophenyl)-1,3-dihydroisobenzofuran-5-carbonitrile,

1-[3-[[3-(5-Chloro-1*H*-indol-3-yl)propyl]ethylamino]propyl]-1-(4-fluorophenyl)-1,3-dihydroisobenzofuran-5-carbonitrile,

1-[3-[[3-(5,7-Difluoro -1*H*-indol-3-yl)propyl]ethylamino]propyl]-1-(4-fluorophenyl)-1,3-dihydroisobenzofuran-5-carbonitrile,

1-[3-[[2-(5-Bromo -1*H*-indol-3-yl)ethyl]methylamino]propyl]-1-(4-fluorophenyl)-1,3-dihydroisobenzofuran-5-carbonitrile,

1-[3-[[3-(5-Bromo -1*H*-indol-3-yl)propyl]methylamino]propyl]-1-(4-fluorophenyl)-1,3-dihydroisobenzofuran-5-carbonitrile,

1-[3-[[2-(5-Bromo -1*H*-indol-3-yl)ethyl]ethylamino]propyl]-1-(4-fluorophenyl)-1,3-dihydroisobenzofuran-5-carbonitrile,

1-[3-[[4-(5-Bromo -1*H*-indol-3-yl)butyl]methylamino]propyl]-1-(4-fluorophenyl)-1,3-dihydroisobenzofuran-5-carbonitrile,

1-[3-[[3-(5-Bromo -1*H*-indol-3-yl)propyl]methylamino]propyl]-1-(4-fluorophenyl)-1,3-dihydroisobenzofuran-5-carbonitrile,

1-[3-[Ethyl[2-(5-iodo -1*H*-indol-3-yl)ethyl]amino]propyl]-1-(4-fluorophenyl)-1,3-dihydroisobenzofuran-5-carbonitrile,

1-[3-[Ethyl[3-(5-iodo -1*H*-indol-3-yl)propyl]amino]propyl]-1-(4-fluorophenyl)-1,3-dihydroisobenzofuran-5-carbonitrile,

1-[2-[[4-(5-Chloro -1*H*-indol-3-yl)butyl]methylamino]ethyl]-1-(4-fluorophenyl)-1,3-dihydroisobenzofuran-5-carbonitrile,

1-[2-[[4-(5-Bromo -1*H*-indol-3-yl)butyl]methylamino]ethyl]-1-(4-fluorophenyl)-1,3-dihydroisobenzofuran-5-carbonitrile,

1-[4-[[2-(5,7-Difluoro -1*H*-indol-3-yl)ethyl]methylamino]butyl]-1-(4-fluorophenyl)-1,3-dihydroisobenzofuran-5-carbonitrile,

1-[4-[[2-(7-Chloro -1*H*-indol-3-yl)ethyl]methylamino]butyl]-1-(4-fluorophenyl)-1,3-dihydroisobenzofuran-5-carbonitrile,

1-[4-[[2-(5-Chloro -1*H*-indol-3-yl)ethyl]methylamino]butyl]-1-(4-fluorophenyl)-1,3-dihydroisobenzofuran-5-carbonitrile,

1-[4-[[2-(5-Bromo -1*H*-indol-3-yl)ethyl]methylamino]butyl]-1-(4-fluorophenyl)-1,3-dihydroisobenzofuran-5-carbonitrile,

1-[4-[[2-(5-Methyl -1*H*-indol-3-yl)ethyl]methylamino]butyl]-1-(4-fluorophenyl)-1,3-dihydroisobenzofuran-5-carbonitrile,

1-[4-[[2-(5-Iodo -1*H*-indol-3-yl)ethyl]methylamino]butyl]-1-(4-fluorophenyl)-1,3-dihydroisobenzofuran-5-carbonitrile,

1-[4-[[2-(5-*t*-Butyl -1*H*-indol-3-yl)ethyl]methylamino]butyl]-1-(4-fluorophenyl)-1,3-dihydroisobenzofuran-5-carbonitrile,

1-[4-[[2-(5-*i*-Propyl -1*H*-indol-3-yl)ethyl]methylamino]butyl]-1-(4-fluorophenyl)-1,3-dihydroisobenzofuran-5-carbonitrile,

1-[3-[[2-(5-Methyl -1*H*-indol-3-yl)ethyl](prop-2-en-1-yl)amino]propyl]-1-(4-fluorophenyl)-1,3-dihydroisobenzofuran-5-carbonitrile,

1-[3-[[2-(5-Fluoro -1*H*-indol-3-yl)ethyl](prop-2-en-1-yl)amino]propyl]-1-(4-fluorophenyl)-1,3-dihydroisobenzofuran-5-carbonitrile,

1-[3-[[2-(7-Fluoro -1*H*-indol-3-yl)ethyl](prop-2-en-1-yl)amino]propyl]-1-(4-fluorophenyl)-1,3-dihydroisobenzofuran-5-carbonitrile,

1-[3-[[3-(5-Fluoro -1*H*-indol-3-yl)propyl](prop-2-en-1-yl)amino]propyl]-1-(4-fluorophenyl)-1,3-dihydroisobenzofuran-5-carbonitrile,

1-[3-[[3-(7-Fluoro -1*H*-indol-3-yl)propyl](prop-2-en-1-yl)amino]propyl]-1-(4-fluorophenyl)-1,3-dihydroisobenzofuran-5-carbonitrile,

1-[3-[[2-(5-Chloro -1*H*-indol-3-yl)ethyl](prop-2-en-1-yl)amino]propyl]-1-(4-fluorophenyl)-1,3-dihydroisobenzofuran-5-carbonitrile,

1-[3-[[2-(5,7-Difluoro -1*H*-indol-3-yl)ethyl]-propylamino]propyl]-1-(4-fluorophenyl)-1,3-dihydroisobenzofuran-5-carbonitrile,

1-[3-[[2-[5-(2-Propyl)-1*H*-indol-3-yl]ethyl]-2-propylamino]propyl]-1-(4-fluorophenyl)-1,3-dihydroisobenzofuran-5-carbonitrile,

1-[3-[[3-(4-Fluoro-7-methyl-1*H*-indol-3-yl)propyl](prop-2-en-1-yl)amino]propyl]-1-(4-fluorophenyl)-1,3-dihydroisobenzofuran-5-carbonitrile,

1-[3-[[2-(4-Chloro-7-methyl-1*H*-indol-3-yl)ethyl](prop-2-en-1-yl)amino]propyl]-1-(4-fluorophenyl)-1,3-dihydroisobenzofuran-5-carbonitrile ,

1-[3-[[3-(5-Chloro -1*H*-indol-3-yl)propyl](prop-2-en-1-yl)amino]propyl]-1-(4-fluorophenyl)-1,3-dihydroisobenzofuran-5-carbonitrile,

1-[3-[[2-(5-Pyrrolo[3,2-*h*]-1*H*-quinolin-3-yl)ethyl](prop-2-en-1-yl)amino]propyl]-1-(4-fluorophenyl)-1,3-dihydroisobenzofuran-5-carbonitrile,

1-[3-[[3-(7-Fluoro -1*H*-indol-3-yl)propyl](2-furylmethyl)amino]propyl]-1-(4-fluorophenyl)-1,3-dihydroisobenzofuran-5-carbonitrile,

1-[3-[[4-(7-Carboxy-1*H*-indol-3-yl)butyl](prop-2-en-1-yl)amino]propyl]-1-(4-fluorophenyl)-1,3-dihydroisobenzofuran-5-carbonitrile,

1-[3-[[2-[5-Bromo-1*H*-indol-3-yl]ethyl]-propylamino]propyl]-1-(4-fluorophenyl)-1,3-dihydroisobenzofuran-5-carbonitrile,

1-[3-[[3-(1*H*-Indol-3-yl)propyl](2-phenoxyethyl)amino]propyl]-1-(4-fluorophenyl)-1,3-dihydroisobenzofuran-5-carbonitrile,

1-[3-[[2-(5-Methyl-1*H*-indol-3-yl)ethyl](2-phenoxyethyl)amino]propyl]-1-(4-fluorophenyl)-1,3-dihydroisobenzofuran-5-carbonitrile,

1-[3-[[2-(5-Fluoro-1*H*-indol-3-yl)ethyl](2-phenoxyethyl)amino]propyl]-1-(4-fluorophenyl)-1,3-dihydroisobenzofuran-5-carbonitrile,

1-[3-[[3-(5-Pyrrolo[3,2-*h*]-1*H*-quinolin-3-yl)propyl]- 2-furylmethylamino]propyl]-1-(4-fluorophenyl)-1,3-dihydroisobenzofuran-5-carbonitrile,

1-[3-[[3-(5-Methyl-1*H*-indol-3-yl)propyl](2-phenoxyethyl)amino]propyl]-1-(4-fluorophenyl)-1,3-dihydroisobenzofuran-5-carbonitrile,

1-[3-[[3-(5-Fluoro-1*H*-indol-3-yl)propyl](2-phenoxyethyl)amino]propyl]-1-(4-fluorophenyl)-1,3-dihydroisobenzofuran-5-carbonitrile,

1-[3-[[2-(5,7-Difluoro-1*H*-indol-3-yl)ethyl](2-phenoxyethyl)amino]propyl]-1-(4-fluorophenyl)-1,3-dihydroisobenzofuran-5-carbonitrile,

1-[3-[[4-(5-Pyrrolo[3,2-*h*]-1*H*-quinolin-3-yl)butyl]- 2-furylmethylamino]propyl]-1-(4-fluorophenyl)-1,3-dihydroisobenzofuran-5-carbonitrile,

1-[3-[2-Phenoxyethyl[2-[5-(2-propyl)-1*H*-indol-3-yl]ethyl]amino]propyl]-1-(4-fluorophenyl)-1,3-dihydroisobenzofuran-5-carbonitrile or

1-[3-[[2-(5-Bromo-1*H*-indol-3-yl)ethyl](2-phenoxyethyl)amino]propyl]-1-(4-fluorophenyl)-1,3-dihydroisobenzofuran-5-carbonitrile

or an acid addition salt thereof.

31. A pharmaceutical composition comprising a compound according to claims 1 to 30 or a pharmaceutically acceptable acid addition salt thereof and at least one pharmaceutically acceptable carrier or diluent.

32. The use of a compound according to claims 1 to 30 or a pharmaceutically acceptable acid addition salt thereof for the preparation of a medicament for the treatment of a disorder or disease responsive to the effect of 5-$HT_{1A}$ receptors.

33. The use of a compound according to claim 32 wherein the medicament is for the treatment of depression, psychosis, anxiety disorders, panic disorder, obsessive compulsive disorder, impulse control disorder, alcohol abuse, aggression, ischaemia, senile dementia, cardiovascular disorders and social phobia.

34. A method for the treatment of a disorder or disease of living animal body, including a human, which is responsive to the effect of 5-$HT_{1A}$ receptors comprising administering to such a living animal body, including a human, a therapeutically effective amount of a compound according to claims 1 to 30 or a pharmaceutically acceptable acid addition salt thereof.

35. A method of treatment according to claim 34 where the disorder or disease is depression, psychosis, anxiety disorders, panic disorder, obsessive compulsive disorder, impulse control disorder, alcohol abuse, aggression, ischaemia, senile dementia, cardiovascular disorders or social phobia.

# INTERNATIONAL SEARCH REPORT

International application No.
PCT/DK 99/00676

A. CLASSIFICATION OF SUBJECT MATTER

IPC7: C07D 307/87, A61K 31/343
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC7: C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

SE,DK,FI,NO classes as above

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

| Category* | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|---|---|---|
| A | DE 2657013 A1 (KEFALAS A/S), 28 July 1977 (28.07.77) -- | 1-32 |
| A | GB 1173312 A (KEFALAS A/S), 10 December 1969 (10.12.69) -- | 1-32 |
| A | WO 9518118 A1 (THE UPJOHN COMPANY), 6 July 1995 (06.07.95) -- | 1-32 |

☐ Further documents are listed in the continuation of Box C. ☒ See patent family annex.

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"E" erlier document but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance: the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance: the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

| Date of the actual completion of the international search | Date of mailing of the international search report |
|---|---|
| 29 March 2000 | 17 -04- 2000 |
| Name and mailing address of the ISA/<br>Swedish Patent Office<br>Box 5055, S-102 42 STOCKHOLM<br>Facsimile No. +46 8 666 02 86 | Authorized officer<br>Göran Karlsson/EÖ<br>Telephone No. +46 8 782 25 00 |

Form PCT/ISA/210 (second sheet) (July 1992)

# INTERNATIONAL SEARCH REPORT

International application No.
**PCT/DK 99/00676**

**Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)**

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.: **34-35**
because they relate to subject matter not required to be searched by this Authority, namely:

**A method for treatment of the human or animal body by therapy, see rule 39.1.**

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

**Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)**

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

**Remark on Protest**

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.

# INTERNATIONAL SEARCH REPORT

Information on patent family members

02/12/99

International application No.
PCT/DK 99/00676

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# INTERNATIONAL SEARCH REPORT

Information on patent family members

02/12/99

International application No.
PCT/DK 99/00676

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# Beyond depression: Evaluation of newer indications and off-label uses for SSRIs

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Mitchell D. Feldman, MD, MPhil,
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## Abstract

Although selective serotonin reuptake inhibitors (SSRIs) are prescribed most often for depressive disorders, they are increasingly being used to treat a variety of anxiety disorders and other conditions and have recently gained FDA approval for a number of them. We conducted a qualitative review of the literature for evidence on the utility of SSRIs for these uses beyond depression, and we summarize our findings here. After covering various anxiety disorders in part 1 of this two-part article, this installment covers treatment of alcohol dependence, chronic pain, eating disorders, premenstrual dysphoric disorder, and sexual dysfunction. We focus on the rationale for SSRI use in these conditions, the degree of supportive clinical trial evidence for each use, and indication-specific dosing and safety considerations. We also present recommendations, based on our literature review, on the preferred and alternative SSRIs for each therapeutic use profiled. (*Formulary* 2002;37:312–19.)

As outlined in part 1 of this article (*Formulary* 2002;37:240–51), selective serotonin reuptake inhibitors (SSRIs) have recently accumulated a range of indications beyond the treatment of depression (table 1)[1,2] and are gaining in popularity for various off-label uses. In part 1 we assessed the evidence and made recommendations concerning the use of SSRIs for a variety of anxiety disorders. In this part we turn our attention to a broader range of new uses for SSRIs: treatment of alcohol dependence, chronic pain syndromes, eating disorders, premenstrual dysphoric disorder, and sexual dysfunction.

As in part 1, we present a qualitative review of the evidence supporting these new uses. Every attempt was made to include the most significant randomized controlled trials (RCTs); however, if no RCTs are available, open-label studies are briefly summarized. Although most of the conditions discussed here are unlabeled uses for SSRIs, we attempted to categorize the drugs into first-line, second-line, and alternative agents according to the existing evidence (see table 2).

## ALCOHOL DEPENDENCE

Treatment of alcohol abuse is complex, due to wide interindividual variability in response to pharmacotherapy, high rates of comorbidities with other psychiatric conditions (eg, depression and anxiety disorders), and a host of genetic and environmental variables.[3,4]

Pharmacologic agents are commonly used to treat alcohol withdrawal symptoms, but few are used to treat alcohol dependence. Although dopamine is recognized as an important neurotransmitter in drugs of abuse such as cocaine and ethanol, other neurotransmitters (such as gamma-aminobutyric acid, serotonin, and glutamate) have been found to play roles in the drug reward, craving, and relapse mechanism.[3] Studies show that animals that prefer alcohol have reduced levels of serotonin and its major metabolite, 5-hydroxy-indoleacetic acid.[5] This inverse relationship between serotonin concentration and alcohol craving may explain the rationale for using SSRIs in treating alcohol dependence.

**State of the evidence.** Several studies with fluoxetine, citalopram, and sertraline have suggested that these agents may be useful in reducing alcohol consumption, craving, and/or disease relapse.[6–10] In one of the largest studies (N = 101), high-dose fluoxetine (60 mg/day) in combination with weekly psychotherapy reduced alcohol consumption from baseline in alcoholic patients, but not significantly more than placebo plus psychotherapy.[6] Acute and delayed effects were seen up to 6 months after treatment, although there was no difference between fluoxetine and placebo in abstinence or delay to the first heavy drinking day. In a single-blind study, no overall difference from placebo was seen with similar doses of fluoxetine.[7] Naranjo et al[8] found that fluoxetine (60 mg/day) reduced the average and total number of daily drinks from baseline levels, but no difference from baseline was seen in the number of abstinent days at either 60 mg/day or 40 mg/day. In a separate study, fluoxetine also failed to prevent relapse in severe alcoholics, but a trend toward higher relapse rates was seen in cocaine-dependent alcoholics compared

*continues on page 315*

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with those without dual dependence.[11]

Citalopram demonstrated more favorable outcomes in increasing the percentage of abstinent days and reducing subjective symptoms of alcoholism compared with placebo,[9] but subjects in this small study were treated with 40 mg/day for only 1 week. One of the earliest studies of an SSRI for this use showed that citalopram (40 mg/day) significantly reduced the amount of alcohol consumed per day relative to baseline in nondepressed alcoholics.[12] It also tripled the number of abstinent days and significantly reduced consumption as early as a few days after initiation.[12] Another trial compared citalopram with placebo in combination with psychosocial intervention; despite promising results in the first week, citalopram failed to show differences from placebo in alcohol intake over the course of the 12-week treatment period.[13] Finally, sertraline (200 mg/day) seemed to improve drinking behavior compared with placebo in patients without a history of lifetime depression, but not in those with a past diagnosis of depression.[10]

One of the criticisms of these previous conflicting studies is that different subtypes of alcoholics may respond differently to treatment. Babor et al[14] distinguished between two types of alcoholics, type A and type B, that may explain variation in response. Type B alcoholics, considered to be at higher risk, are characterized by earlier onset of alcohol dependence, more severe dependence, a higher incidence of comorbidities such as depression, and overall poorer prognosis after treatment.

Surprisingly, the first trial that looked at subtypes of alcoholics found that fluoxetine was associated with an increase in the number of drinking days in both type A and type B subjects and in the number of drinks per day in type B subjects.[15] Recently, the same investigators administered flexible doses of sertraline, up to 200 mg/day, to type A and type B alcoholics for 12 weeks.[16] In addition to medication, all subjects received weekly 12-step facilitation therapy. Sertraline improved the percentage of days that drinks were consumed among type A alcoholics, while no improvement was seen in type B subjects in either the sertraline or placebo groups. Type A subjects who received sertraline also showed increased time to relapse compared with their type B counterparts.

Due to negative findings in clinical trials, fluoxetine does not seem to be effective in treating alcohol dependence. Moreover, fluoxetine use may actually worsen drinking behavior in type B alcoholics and therefore should be avoided in this subset of patients.[15]

**Recommendations.** The role of SSRIs in the treatment of alcohol dependence still requires further investigation. Opiate antagonists and disulfiram have been used with some success for alcohol dependence, although there are advantages and disadvantages with each agent.[3] SSRIs may be an alternative in patients who have failed or could not tolerate these traditional agents. In addition, SSRIs may be beneficial in patients who have concomitant diagnosis of alcohol dependence and depression. The duration of SSRI therapy for this use is uncertain, although it is highly dependent on the patient's past and current psychiatric and medical history. Higher doses of fluoxetine, citalopram, and sertraline (than those used in depression) may need to be used in alcohol dependence, based on the literature described previously.

## CHRONIC PAIN

Historically, tricyclic antidepressants (TCAs) have proven fairly effective for the management of various chronic pain syndromes, including migraine headaches, diabetic neuropathy, and others. Their pharmacologic effect for these conditions is believed to be independent of antidepressant properties, occurs

■ Table 1

**Available SSRIs and their FDA-approved indications**

| Drug | Dosage forms and strengths | Approved indications |
|---|---|---|
| Fluoxetine (Prozac, Sarafem, Prozac Weekly, generics) | Prozac<br>Tablets: 10 mg<br>Pulvules: 10, 20, and 40 mg<br>Oral solution: 20 mg/5 ml<br>Sarafem<br>Pulvules: 10, 20, and 40 mg<br>Prozac Weekly<br>Capsules (delayed release): 90 mg<br>Generics<br>Tablets: 10 and 20 mg<br>Capsules: 10, 20, and 40 mg<br>Oral solution: 20 mg/5 ml | Depression, OCD, bulimia nervosa, PMDD |
| Sertraline (Zoloft) | Tablets: 25, 50, and 100 mg<br>Oral concentrate: 20 mg/ml (must be diluted before use) | Depression, OCD, panic disorder, PTSD |
| Paroxetine (Paxil) | Tablets: 10, 20, 30, and 40 mg<br>Oral suspension: 10 mg/5 ml | Depression, OCD, GAD, panic disorder, PTSD, social phobia |
| Fluvoxamine (Luvox, generics) | Luvox and generics<br>Tablets: 25, 50, and 100 mg | OCD |
| Citalopram (Celexa) | Tablets: 20 and 40 mg<br>Oral solution: 10 mg/5 ml | Depression |

OCD = obsessive-compulsive disorder; PMDD = premenstrual dysphoric disorder; PTSD = posttraumatic stress disorder; GAD = generalized anxiety disorder

*Formulary*/Source: Adapted from references 1 and 2

■ Table 2
**Summary of recommendations for reviewed uses/indications***

| | |
|---|---|
| **Alcohol dependence** | No recommendation |
| **Chronic pain** | |
| **Diabetic neuropathy** | ■ First line—no recommendation<br>■ Second line—citalopram, paroxetine |
| **Fibromyalgia** | ■ First line—no recommendation<br>■ Second line—fluoxetine |
| **Headache syndromes** | ■ First line—no recommendation<br>■ Second line—fluoxetine, fluvoxamine<br>■ Alternative—citalopram, paroxetine, sertraline |
| **Eating disorders** | |
| **Bulimia nervosa** | ■ First line—fluoxetine<br>■ Second line—fluvoxamine |
| **Anorexia nervosa** | ■ First line—no recommendation<br>■ Second line—fluoxetine |
| **Binge-eating disorder** | ■ First line—no recommendation<br>■ Second line—fluoxetine, sertraline |
| **Premenstrual dysphoric disorder** | ■ First line—citalopram, fluoxetine, fluvoxamine, paroxetine, sertraline |
| **Sexual dysfunction** | |
| **Premature ejaculation** | ■ First line—no recommendation<br>■ Second line—paroxetine<br>■ Alternative—citalopram, fluoxetine, fluvoxamine, sertraline |

* **First line** = Agents that are FDA-approved for the indication and/or have an adequate number of well-designed randomized controlled trials (RCTs) and good tolerability. **Second line** = Agents with a few RCTs limited by inadequate design/small sample size or a large number of open-label studies suggesting efficacy, and/or with less tolerability than first-line agents or inconvenient dosing for the indication. **Alternative** = Agents with no published RCTs, no supportive evidence from RCTs, or only a few supportive open-label studies; these agents also have significant problems with administration or tolerability for the indication. Agents within each recommendation category are listed in alphabetical order.

*Formulary*/Source: K.C. Lee, PharmD, M.D. Feldman, MD, and P.R. Finley, PharmD

at comparatively lower doses, and has a relatively rapid onset. While most experts feel that antidepressants that enhance norepinephrine and serotonin are most effective, some preliminary evidence suggests that SSRIs may have a role in managing certain types of chronic pain.[17]

**Headache syndromes.** Seven double-blind, placebo-controlled trials have been published that collectively suggest that SSRIs may relieve migraine or tension headache syndromes (three studies with fluoxetine, two with fluvoxamine, and one each with citalopram and paroxetine).[18–24] Only two of these studies compared an SSRI (citalopram or fluvoxamine) with a TCA (amitriptyline).[21,22] While both fluvoxamine and amitriptyline reduced migraine attacks in the one trial,[22] results of the other study favored the dual-action TCA over citalopram.[21]

Additional open-label or retrospective trials with SSRIs have reported benefits, however, including two studies among patients in whom treatment with TCAs and monoamine oxidase inhibitors had failed.[25,26] While the precise role of SSRIs in managing headache pain remains undefined, this preliminary evidence may prompt additional studies comparing SSRIs and TCAs.

**Diabetic neuropathy.** Several studies have evaluated the analgesic effects of SSRIs in treating diabetic neuropathy. One notable crossover study reported that the TCA amitriptyline (average dose of 105 mg/day) was considerably more effective than fluoxetine (40 mg daily), as the two agents yielded moderate or greater pain relief in 74% and 48% of patients, respectively.[27] Investigations comparing paroxetine with TCAs have shown similar efficacy between these agents, although the beneficial effects of the SSRI were only evident once higher plasma concentrations were achieved.[28,29] A small placebo-controlled study of citalopram (40 mg/day) demonstrated mild to moderate pain relief that did not appear to be associated with plasma concentrations of the drug.[30]

**Other types of chronic pain.** Preliminary investigations of SSRIs for other pain syndromes have met with mixed results. For the treatment of fibromyalgia, fluoxetine and amitriptyline both appeared to be significantly more effective than placebo and exhibited superior effects when administered together.[31] A placebo-controlled study of citalopram (20 to 40 mg/day) failed to reveal statistically significant differences in fibromyalgia outcomes.[32] Fluoxetine (20 mg/day) was reported to be comparable to amitriptyline for treating low back pain in one study[33] and superior to amitriptyline for treatment of rheumatic pain in another.[34] In contrast, citalopram was found to be much less effective for low back pain than the noradrenergic antidepressant maprotiline.[35] Clearly, definition of the SSRIs' role in managing chronic pain awaits future well-controlled investigations in nondepressed patient populations.

## EATING DISORDERS

Shortly after fluoxetine's launch in this country, a variety of case reports began documenting weight loss in depressed subjects. These reports generated considerable optimism about the anorectic properties of SSRIs. Long-term studies ultimately showed that most patients returned to their baseline body weight with chronic fluoxetine administration. As a class, SSRIs are now considered to be weight-neutral, with the notable exception of paroxetine, which has been shown to induce significant weight gain (defined as an increase of 7% or more)

in approximately 25% of depressed patients.[36] Nonetheless, SSRIs have been used with variable success to treat other eating disorders.

**Bulimia nervosa.** Although psychotherapy is generally regarded as the treatment of choice for bulimia nervosa, a wide variety of antidepressants appear to be quite helpful as adjunctive treatment for reducing binge-eating behavior. Among the SSRIs, fluoxetine has shown the most promise and is, in fact, the only SSRI to gain FDA approval for this indication. Short- and long-term studies have shown that fluoxetine can reduce binge-eating behavior,[37,38] and this effect is generally believed to be independent of effects on mood. While the relationship of dose to response in bulimia has not been extensively studied, one investigation found superior response rates and good tolerability with fluoxetine doses of 60 mg daily as compared with 20 mg daily or placebo.[39] The only other SSRI to be evaluated for the management of bulimia has been fluvoxamine, which was found to significantly reduce relapse rates compared with placebo.[40]

**Anorexia nervosa.** The therapeutic effects of SSRIs on anorexia nervosa have not been forthcoming. While hospitalization remains the most efficacious intervention for reestablishing healthy nutritional status, this option is obviously expensive, prompting the search for other remedies. Early efforts to treat anorexia with antidepressants met with disappointing results, but more recent studies have shown SSRIs to be quite effective, particularly if administered after weight restoration has occurred.[41,42] One potential explanation for this response pattern is that anorexic patients do not have sufficient dietary intake or body stores of serotonin precursors (ie, l-tryptophan) at baseline to support the basic pharmacologic action of antidepressants. Subsequent studies of fluoxetine in patients who have regained their ideal body weight have reported comparatively high remission rates and reductions in obsessive and compulsive behavior.

**Binge-eating disorder.** While binge-eating behaviors are always associated with bulimia nervosa and sometimes encountered with anorexia nervosa, binge-eating disorder is a distinct psychiatric condition distinguished from other eating disorders by the absence of compensatory weight loss measures (eg, vomiting, laxative abuse). The evidence supporting SSRI benefits specifically for binge-eating disorder is very limited. In a 6-week study, McElroy et al reported a significant reduction in binge-eating behavior with sertraline as compared with placebo, as well as improvement in overall psychopathology; the average daily sertraline dose was 189 mg.[43] In a 52-week placebo-controlled study of obese patients, fluoxetine (in combination with behavioral therapy) was found to be much more effective at inducing weight loss than behavioral therapy alone.[44] There was no difference in benefit, however, among patients who had binge-eating histories and those who did not.[44]

## PREMENSTRUAL DYSPHORIC DISORDER

Premenstrual dysphoric disorder (PMDD) is widely recognized as a distinct and cyclical mental illness that afflicts 3% to 8% of women, exclusively during their reproductive years. It is considered a more severe form of premenstrual syndrome (PMS) and is associated with a high degree of social and occupational impairment.[45] By definition, the physical and mental symptoms of PMDD are manifest during the luteal phase and remit shortly after the onset of menses.

The pathophysiology of PMDD remains unclear. Most women with PMDD, for instance, have quantitatively normal fluctuations in gonadal hormones, but their response to the cyclic changes is most pronounced. As the diagnostic criteria for PMDD contain many symptoms suggestive of depressive or anxiety disorders, a serotonin deficiency has been theorized as a final common pathway.[46] Acute dietary depletion of a serotonin precursor (l-tryptophan) has been shown to aggravate premenstrual symptoms, and the superior efficacy of serotonergic antidepressants in treating PMDD further supports this explanation.[47]

Treatment of PMDD is largely contingent on the severity or urgency of symptoms. While mild illness may respond to exercise, dietary modification, or calcium supplementation, more severe symptoms appear to be uniquely responsive to SSRIs (or other serotonergic agents).

**State of the evidence.** To date, more than 40 studies have been published documenting the efficacy of SSRIs for relief of physical symptoms (eg, headache, bloating, breast tenderness) as well as mood fluctuations (eg, irritability, anxiety, melancholia). A recent meta-analysis of 15 RCTs studying SSRIs for the treatment of severe PMS concluded that this antidepressant class was significantly more effective than placebo in reducing overall PMS symptoms, with an overall mean difference of −1.066 in favor of SSRIs (95% CI, −1.38 to −0.75), corresponding to an odds ratio of 6.9.[48]

> ■ While fluoxetine is the only SSRI approved for premenstrual dysphoric disorder, all have demonstrated efficacy in published trials.

**Recommendations.** While fluoxetine is the only SSRI approved by the FDA for this indication, all have demonstrated efficacy in published trials.[48]

Although the benefit of SSRIs for PMDD has been demonstrated in short- and long-term studies, the onset of therapeutic effects is much more rapid than that reported for depression. Statistically significant differences in baseline symptoms have been demonstrated within 3 to 4 days of treatment initiation,[49] implying that the mechanism responsible for PMDD relief may be subtly distinct from that for depression. Blinded studies have also shown that these benefits may be achieved even if the SSRI is administered only during

the 7- to 14-day period immediately before menses (ie, the intermittent to late luteal phase).[49,50] This dosing method may be preferred from the standpoint of cost as well as advantages in tolerability and medication adherence.

The doses of SSRIs used in PMDD studies have been comparable to those used for depression. In a seminal study of fluoxetine, for instance, 20 mg/day was comparable in efficacy to 60 mg/day, but the higher dose was associated with a much higher dropout rate due to adverse effects.[51] Anecdotal reports of poor tolerability with SSRIs among women with PMDD have not been confirmed in fixed-dose trials, but future studies of low-dose SSRI therapy are clearly indicated.

The duration of SSRI treatment for PMDD is always patient-specific and largely influenced by the presence or absence of environmental triggers (eg, domestic issues, dietary imbalances, overall health status). It should be emphasized, however, that the therapeutic benefits of SSRIs will be lost immediately upon discontinuation (in contrast to treatment termination for depressive illness). Furthermore, PMDD symptoms often worsen over time until relief is ultimately provided by the onset of menopause.

## SEXUAL DYSFUNCTION

Sexual dysfunction is a common and disruptive condition associated with depression as well as with SSRI therapy. While SSRIs are commonly implicated for difficulty achieving orgasm, depression itself has been associated with a decrease in libido for more than 50% of patients.[52] Therefore, certain aspects of sexual function (ie, libido) may actually improve with the onset of an SSRI's therapeutic antidepressant effects.

Of these two types of sexual dysfunction, the influence of SSRIs on orgasm is much more notorious and problematic. Approximately 30% to 50% of patients receiving any SSRI report a significant delay in orgasm or ejaculation. Although most patients find delayed orgasm to be an undesirable effect, this side effect can serve to successfully treat men suffering from premature ejaculation (often defined as an intravaginal ejaculatory latency time [IELT] of less than 60 seconds).[53] At least four double-blind, placebo-controlled studies have shown SSRI treatment to successfully prolong time to ejaculation in men with documented premature ejaculation.[54–57] Studies of single-dose administration have found that while all SSRIs can prolong latency time, paroxetine has the most profound effect, increasing the IELT by more than 600%, on average.[57] Ejaculatory delay with SSRIs appears to be a dose-dependent phenomenon; with the exception of one positive open-label investigation with low-dose sertraline (25 mg), low doses have not been vigorously studied.[58]

## CONCLUSION

Among the newer uses of SSRIs reviewed in this second installment of our two-part article, only premenstrual dysphoric disorder and bulimia nervosa have consistently been shown to be effectively treated with SSRIs. There is less evidence for the use of SSRIs in alcohol dependence, chronic pain syndromes (diabetic neuropathy, fibromyalgia, headache syndromes, low back pain), anorexia nervosa, and binge-eating disorder. The efficacy and tolerability of SSRIs in these latter uses need to be further investigated with randomized, placebo-controlled trials. While SSRIs appear to be beneficial in treating premature ejaculation, their association with undesirable orgasm delay in other patients leaves their role in sexual dysfunction highly subject to individual patient circumstances.

Although clinicians may be compelled to choose one SSRI over another based on FDA-approved labeling, a patient's psychiatric and medical history, concurrent medications, and preference should also be considered, as well as the tolerability profile and cost of individual SSRIs.

## DISCLOSURE

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# Off-Label Applications for SSRIs

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**Selective serotonin reuptake inhibitors (SSRIs) are widely used because of their safety, tolerability, and demonstrated efficacy across a broad range of clinical conditions. Medical literature supports the use of SSRIs for the treatment of many conditions outside of the indications approved by the U.S. Food and Drug Administration. SSRIs offer a reasonable alternative to traditional therapy for generalized anxiety disorder. A side effect of SSRIs coincidentally provides therapy for premature ejaculation. SSRIs may reduce the frequency and severity of migraine headaches and are possibly effective in reducing the pain of diabetic neuropathy. When taken in combination with tricyclic antidepressants, SSRIs offer more potent therapy for fibromyalgia than either agent alone. SSRIs appear to be effective in some patients with neurocardiogenic syncope that is refractory to standard therapies. Clinical experience supported by ongoing research continues to expand on the broad array of therapeutic applications for this class of medication. (Am Fam Physician 2003;68:498-504.**


*Members of various family practice departments develop articles for "Practical Therapeutics." This article is one in a series coordinated by the Department of Family Medicine at Naval Hospital Jacksonville, Jacksonville, Fla. Guest editor of the series is Anthony J. Viera, LCDR, MC, USNR.*

Selective serotonin reuptake inhibitors (SSRIs) were initially developed to relieve depression and have become the most commonly prescribed class of antidepressants.[1] SSRIs block the reuptake of serotonin at the presynaptic neuron, with minimal or no effect on norepinephrine or dopamine. This narrow mechanism of action confers similarity of efficacy and tolerability with few side effects.[1]

The following five SSRIs have been approved by the U.S. Food and Drug Administration (FDA) for use in the United States: citalopram (Celexa), fluoxetine (Prozac), fluvoxamine (Luvox), paroxetine (Paxil), and sertraline (Zoloft). Although the FDA has approved these SSRIs for treatment of a variety of conditions, the medical literature supports their use for a number of "off-label" indications. Off-label use does not imply improper or illegal use.[2] The FDA cannot give approval for further indications until it has reviewed new efficacy and safety data provided by the pharmaceutical companies.

The use of a well-documented therapy that lacks a specific "labeling" should not be precluded. The decision to prescribe a given medication should be based on the available evidence and a careful consideration of the potential risks and benefits in the context of the individual patient.

This article reviews the use of SSRIs for six conditions commonly managed by family physicians: generalized anxiety disorder, premature ejaculation, migraine headache, diabetic neuropathy, fibromyalgia, and neurocardiogenic syncope *(Table 1)*.[3-20]

## Generalized Anxiety Disorder

Generalized anxiety disorder (GAD) is one of the most prevalent psychiatric disorders. Benzodiazepines such as diazepam (Valium), alprazolam (Xanax), and clonazepam (Klonopin), which are used to treat GAD, can cause sedation, difficulty concentrating, and other bothersome side effects. Dependence can develop, leading to withdrawal symptoms on discontinuation of these agents. Buspirone (BuSpar), a nonbenzodiazepine anxiolytic that does not lead to dependence, is an effective alternative, but it must be taken three times daily.[21]

SSRIs have been prescribed safely and effectively for mixed anxiety and depression syndromes, as well as for social anxiety.[22] Paroxetine may be effective for GAD treatment.[5] [Evidence level A, randomized controlled trial (RCT)]

*See page 406 for definitions of strength-of-evidence levels.*

***See editorial on page 425.***

TABLE 1
**Off-Label Applications of SSRIs**

| *Condition* | *Medication and recommended dosages* | *Efficacy/recommendations* | *Level of evidence* |
|---|---|---|---|
| Generalized anxiety disorder | Fluvoxamine (Luvox), 50 to 300 mg daily[3,4] | Effective; may be a good long-term alternative to benzodiazepines or other anxiolytics | A: RCT |
| | Paroxetine (Paxil), 20 to 60 mg daily (generalized anxiety disorder is not an off-label use)[5] | — | A: RCT |
| Premature ejaculation | Paroxetine, 20 mg daily or as needed a few hours before anticipated sexual activity[6,7] | Effective; consider as first-line treatment | A: RCT |
| | Sertraline (Zoloft), 25 to 50 mg daily or as needed a few hours before anticipated sexual activity[6,8,9] | | |
| | Fluoxetine (Prozac), 20 mg daily[6] | | |
| Migraine headaches (prophylaxis) | Fluoxetine, 20 to 40 mg daily[10-12] | May be useful if patient cannot use standard prophylactic agents or if other agents fail; good choice if patient has concomitant depression or other illness treatable with SSRI | A: RCT |
| Diabetic neuropathy | Paroxetine, 40 mg daily[13] | Possibly effective; other drugs should be considered first. One meta-analysis found no difference between placebo and SSRIs | B: lower quality RCT |
| Fibromyalgia | Fluoxetine, 20 mg daily[14,15] | Possibly effective, particularly when combined with amitriptyline (Elavil) | B: lower quality RCT |
| | Citalopram (Celexa), 20 to 40 mg daily[16,17] | Studies on citalopram showed no significance | B: lower quality RCT |
| Neurocardiogenic syncope | Paroxetine, 20 mg daily[18] | May be useful if standard treatments fail | A: RCT |
| | Sertraline, 50 mg daily[19] | Has been studied in children | B: nonrandomized, small, prospective trial |
| | Fluoxetine, 20 mg daily[20] | — | B: nonrandomized, small, prospective trial |

*SSRIs = selective serotonin reuptake inhibitors; RCT = randomized controlled trial.*

*Information from references 3 through 20.*

*Delayed or inhibited ejaculation, a known side effect of SSRIs, has made SSRIs potentially useful in the management of premature ejaculation.*

In the trial,[5] 81 patients were randomized to treatment with paroxetine (20 mg daily), imipramine (Tofranil), or the benzodiazepine 2'chlordesmethyldiazepam. The patients had a diagnosis of GAD according to criteria in the *Diagnostic and Statistical Manual of Mental Disorders*, 4th ed (DSM-IV), a score of at least 18 on the Hamilton Rating Scale for Anxiety (HRSA), and no comorbid psychiatric conditions. The patients ranged from 18 to 65 years of age. Demographics were similar in each group. Sixty-three patients (77.7 percent) completed the study. Using the HRSA to measure response, 68 percent of the patients in the paroxetine group, 72 percent in the imipramine group, and 55 percent in the 2'chlordesmethyldiazepam group had at least a 50 percent decrease in HRSA score by the end of the eight-week study. Paroxetine was recently approved by the FDA for GAD treatment.

SSRIs may be particularly useful in the treatment of GAD in pediatric patients.[3] [Evidence level A, RCT] In a multicenter, double-blind trial, 128 children six to 17 years of age with social phobia, separation anxiety disorder, or GAD (as defined by DSM-IV) were randomized to treatment with fluvoxamine or placebo.[3] All had received three weeks of psychotherapy without showing improvement. Fluvoxamine was chosen because it was the only SSRI approved by the FDA for use in children in 1996 when the study was designed. Fluvoxamine therapy (at a maximum dosage of 300 mg daily) resulted in a statistically significant decrease in scores on the Pediatric Anxiety Rating Scale compared with placebo. Although this trial was not specific to GAD, it was noted that anxiety disorders in children typically occur together, thereby making it difficult to isolate one disorder for study.

SSRIs seem particularly suited for use in older patients with anxiety disorders.[4] [Evidence level B, nonrandomized trial] In a small, open-label trial, patients more than 50 years of age with GAD, panic disorder, or obsessive-compulsive disorder were treated with fluvoxamine (median dose, 200 mg daily).[4] Twelve of 19 patients (63 percent) completed the 21-week study, with eight of the 12 (66.6 percent) achieving a 50 percent reduction in symptoms as measured by standardized scales. The existence of comorbid depression, as well as the confounding variable of therapy combined with benzodiazepines, were two further limitations of this trial. The authors conclude that randomized, placebo-controlled trials are warranted to study the use of SSRIs for treatment of anxiety disorders in the older population.

## Premature Ejaculation

Though premature ejaculation has been overshadowed by recent attention given to erectile dysfunction, it is the most prevalent form of male sexual dysfunction.[23] Delayed or inhibited ejaculation, a known side effect of SSRIs, has made SSRIs potentially useful in the treatment of this disorder. The ejaculation-delaying effect was analyzed in a double-


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blind, placebo-controlled trial completed by 51 men.[6] Fluoxetine, sertraline, and paroxetine have been found to increase the latent period of intravaginal ejaculation and therefore to be beneficial in patients who prematurely ejaculate.[6] [Evidence level A, RCT] Fluvoxamine had the least effect in increasing ejaculatory latency, a difference that was not statistically significant compared with placebo. Citalopram was not studied.

It was demonstrated in a second study[6] that SSRI-induced ejaculation delay is probably an effect independent of the baseline ejaculatory latency time.

In a study of 46 men 22 to 63 years of age who prematurely ejaculate (with a baseline mean ejaculatory interval of less than one minute), sertraline increased the ejaculatory interval in a dose-dependent fashion.[8] At 25 mg daily, sertraline increased the mean ejaculatory interval to 7.6 minutes with the fewest side effects and with no men experiencing anejaculation. At 50 mg daily, the mean ejaculatory interval increased to 13.1 minutes with four men experiencing anejaculation and two men experiencing minor side effects (drowsiness, anorexia, dyspepsia). At 100 mg daily, the mean ejaculatory interval increased to 16.4 minutes, but 10 men experienced anejaculation and two men experienced erectile dysfunction and decreased libido.

Studies also show that SSRIs, particularly sertraline[9] and paroxetine,[7] can probably be used on an as-needed basis and taken a few hours before anticipated sexual activity. [Reference 9—Evidence level B, nonrandomized trial; Reference 7—Evidence level B, randomized crossover trial]

## Migraine Headache Prophylaxis

There is fair support for the effectiveness of SSRIs in migraine prophylaxis. Prophylactic treatments for migraine headaches have included tricyclic antidepressants, beta-adrenergic blockers, and calcium channel blockers. These medications are frequently associated with an unfavorable side effect profile and may not be well tolerated by a significant number of patients with migraines. Because most theories of migraine pathophysiology focus on altered serotonergic metabolism, and given the favorable tolerability of SSRIs, the use of SSRIs in migraine prophylaxis has been studied.[10-12,24] While published results are promising, most authors acknowledge that these studies are only preliminary.

*Three randomized, double-blind, placebo-controlled studies showed a decrease in the frequency and severity of migraine headaches with fluoxetine therapy.*

Most studies used fluoxetine. Of these, at least four were randomized, double-blind, placebo-controlled studies.[10-12,24] Three of these four studies showed a significant decrease ($P < .05$) in the frequency and severity of headaches.[10-12] [References 10, 11, and 12—Evidence level A, RCT] The patients ranged from 18 to 65 years of age, and the minimum frequency of migraines ranged from more than one per month to more than one per week. Daily dosages of fluoxetine ranged from 20 to 40 mg in these studies.

Evidence is limited regarding the use of the other SSRIs in migraine headache treatment. One randomized comparison study of fluvoxamine and amitriptyline (Elavil) showed that fluvoxamine decreased the number of migraine attacks as effectively as amitriptyline.[25] [Evidence level B, double-blind comparison]

## Diabetic Neuropathy

Tricyclic antidepressants are well established as effective therapy for the symptoms of diabetic neuropathy.[26,27] Although mexiletine (Mexitil), capsaicin (Zostrix), carbamazepine (Tegretol), and gabapentin (Neurontin) are among other therapies that have been shown to be effective in treating neuropathic pain, no single medication has proved to be consistently effective.[28-31] SSRIs should not be considered as first-line therapy for diabetic neuropathy; the

*SSRIs should not be considered as first-line therapy for diabetic neuropathy, because the evidence for their use for this purpose is limited.*

evidence for their use is fair and indicates that SSRIs may be only possibly effective.

A randomized, double-blind, crossover study of 29 patients found both imipramine (50 to 75 mg daily) and paroxetine (40 mg daily) to be superior to placebo.[13] [Evidence level B, lower quality RCT] Imipramine, however, was significantly better than paroxetine for relieving nearly all symptoms, including pain and sleep disturbance.

However, one study did not find SSRIs to be superior to placebo in relieving painful neuropathy.[32] [Evidence level A, meta-analysis] The meta-analysis of RCTs compared the efficacy and adverse effects of antidepressants and anticonvulsants in treating neuropathic pain, including diabetic neuropathy. Overall, for every three patients treated with a tricyclic antidepressant or an anticonvulsant, one experienced a 50 percent reduction in pain (number needed to treat [NNT] of three). While the authors noted the lack of statistically significant improvement using the pooled data of SSRIs, they thought the data insufficient to "draw a robust conclusion."[32]

Another review of RCTs found SSRIs to be helpful in treating diabetic neuropathy but confirmed that they are not as efficacious as other therapies.[33] [Evidence level B, nonquantitative systematic review] An NNT of 1.4 was calculated for imipramine, compared with the NNT of 2.4 calculated from other studies of tricyclic antidepressants. The NNT was 1.9 for dextromethorphan (Delsym), 3.3 for carbamazepine, 3.4 for tramadol (Ultram) and levodopa (Larodopa), 3.7 for gabapentin, 5.9 for capsaicin, 6.7 for SSRIs, and 10.0 for mexiletine. It was cautioned that, with the exception of the tricyclic antidepressants, these numbers were calculated on the basis of few trials or small total patient numbers per drug.

## Fibromyalgia

Fibromyalgia is the most common rheumatic cause of chronic pain.[34] Medications most commonly prescribed are tricyclic antidepressants, SSRIs, muscle relaxants, simple analgesics, and nonsteroidal anti-inflammatory drugs.[35] Pharmacologic therapies have shown only modest benefit at best. A meta-analysis of 49 studies found exercise and cognitive behavior therapy to be more efficacious than pharmacologic treatment alone.[36] [Evidence level A, meta-analysis] The results of the few RCTs involving SSRIs have been mixed.

Two small trials of citalopram (20 to 40 mg daily) failed to reach significance, although there were subtle trends toward improvements in sleep, pain, and functioning.[16,17] [References 16 and 17—Evidence level B, lower quality RCTs] A trial of fluoxetine (20 mg daily) did not show significant improvement after six weeks of therapy, but the study was limited by a 43 percent dropout rate from an initially small sample of 42 patients.[14] [Evidence level B, lower quality RCT]

Conversely, a crossover, placebo-controlled trial comparing fluoxetine (20 mg daily) and amitriptyline (25 mg daily) demonstrated significant improvement in global well-being, pain, and sleep for each medication alone, and further improved efficacy when the two were used in combination.[15] [Evidence level B, lower quality RCT] Nineteen of 31 initial participants (61 percent) completed each of four six-week trials separated by two-week washout periods. Significant improvement was noted by 63 percent of those taking the combination compared with 32 percent and 24 percent of patients taking a single agent. The effects were independent of coexistent depression. The study was limited by the dropout rate and has not been duplicated.

Although the Cochrane Musculoskeletal Group is performing a systematic review to

assess the efficacy of SSRIs versus placebo and other antidepressants, it is clear that further study is necessary.[37] Currently, SSRIs, with or without tricyclic antidepressants, can be viewed as only possibly effective in patients with unsatisfactory responses to nonpharmacologic therapy.

## Neurocardiogenic Syncope

SSRIs appear to be an effective treatment in neurocardiogenic syncope refractory to standard therapies. Neurocardiogenic syncope, or vasovagal syncope, is a common disorder of transient autonomic nervous system dysfunction.[38] Although no definitive treatment for neurocardiogenic syncope exists, standard therapies such as atenolol (Tenormin) and midodrine (ProAmatine) have demonstrated efficacy. Fludrocortisone (Florinef) and increased salt and fluid intake are commonly used as well.[38]

One randomized, double-blind, placebo-controlled study involved the use of paroxetine in the treatment of neurocardiogenic syncope refractory to standard therapies.[18] [Evidence level A, RCT] Paroxetine (20 mg daily) was found to significantly improve symptoms in patients refractory to or intolerant of standard treatments. Of the 68 patients in the study, all of whom had a documented positive head-up tilt test initially, 61.8 percent in the paroxetine group versus 38.2 percent in the placebo group had negative tilt table tests after one month. During the approximately two-year follow-up period, spontaneous syncope occurred in 17.6 percent in the paroxetine group compared with 52.9 percent in the placebo group. Paroxetine was generally well tolerated.

Smaller, nonrandomized, prospective studies (two involving pediatric patients) involved the use of sertraline and fluoxetine in the treatment of refractory neurocardiogenic syncope.[19,20,39] Each of these agents showed promising results, with most patients having a negative repeat tilt test or remaining symptom-free for at least six months.

*The opinions and assertions contained herein are the private views of the authors and are not to be construed as official or as reflecting the views of the U.S. Navy Medical Corps or the U.S. Navy at large.*

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# Treatment of abdominally obese men with a serotonin reuptake inhibitor: a pilot study.

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OBJECTIVE: To investigate the effects of a selective serotonin reuptake inhibitor (SSRI) on the neuroendocrine and autonomic nervous system perturbations found in abdominal obesity. DESIGN: Treatment for 6 months with citalopram and for 6 months with placebo using a double-blind, cross-over design, with a 2-month wash-out period between treatment periods. SUBJECTS: Sixteen healthy men, 45-60 years, moderately obese and with an abdominal fat distribution. MEASUREMENTS: Anthropometry, three different depression rating scales, serum lipids, testosterone, IGF-I, oral glucose tolerance test (OGTT), pituitary stimulation with corticotropin releasing hormone (CRH), arithmetic stress test, and excretion of cortisol and metoxycatecholamines in urine, collected during 24 h. RESULTS: Cortisol concentrations in the morning were low before treatment, indicating a perturbed function of the hypothalamic-pituitary-adrenal (HPA) axis. After treatment with citalopram morning cortisol concentrations rose to normal. Cortisol concentrations after stimulation with CRH or stress were elevated by citalopram treatment, but urinary cortisol excretion was unchanged. The glucose concentrations after OGTT (120 min) tended to be reduced, with unchanged insulin concentrations, whilst other metabolic values did not change during treatment. Heart rate after administration of CRH, and during laboratory stress test, decreased by treatment with citalopram. Diurnal urinary excretion of metoxycatecholamines tended to decrease. Neither body mass index nor waist/hip circumference ratio decreased. Depression scores were within normal limits before treatment and did not change. CONCLUSION: The results of this pilot study indicate improvements in the regulation of neuroendocrine-autonomic systems as well as metabolism in abdominal obesity during treatment with an SSRI.

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# Sertraline enhances the effects of cognitive-behavioral treatment on weight reduction of obese patients.

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Serotonin reuptake inhibitors, such as dexfenfluramine, fluoxetine and fluvoxamine, have been proposed as therapeutical tools for the treatment of eating disorders and obesity. Sertraline, a SSRI used in the treatment of depression, interferes with eating behavior in animal models, but it has not been tested in obese humans. Aim of this study is the assessment of the effects of sertraline on eating attitudes and body weight in obese patients with and without mood disorders. A consecutive series of 65 obese out-patients aged 18-65 years, with a body mass index (BMI) > 30 kg/m2, was treated for 6 months with sertraline 150 mg/day per os, in addition to a cognitive-behavioral treatment (CBT). A consecutive series of 60 obese patients with similar characteristics, who were treated with CBT only, were used as control group. A greater reduction of BMI (mean +/- SD) was observed in sertraline-treated patients when compared to controls (from 35.3 +/- 5.7 to 32.0 +/- 5.4 kg/m2 in sertraline-treated patients, from 37.1 +/- 7.0 to 36.0 +/- 7.1 kg/m2 in controls; 6.5 +/- 5.4% vs. 3.0 +/- 6.3%; $p < 0.01$), while a similar change in eating attitudes (evaluated through the BITE questionnaire) was observed in both groups. Effects of sertraline on eating attitude and body weight were similar in patients with and without mood disorders. In conclusion, sertraline, administered together with CBT, seems to be more effective in inducing weight loss in obese patients when compared with CBT alone, and therefore it could be a useful tool in the first months of CBT for severe obesity.

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